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Prophylactic Treatment of an Experimental Arteriosclerosis With Magnesium and Potassium Salts

Hans Selye, M.D., Montreal, Canada

It was observed a short time ago that rats treated concurrently with suitable doses of 2α-methyl-9α-chlorocortisol (Me-Cl-COL) and NaH_2PO_4 invariably succumb with the clinical manifestations of acute cardiac death, and at autopsy exhibit large, yellowish, infarct-like, necrotic patches in their myocardium.[1,2] The literature on this "infarctoid cardiopathy" has been the subject of a recent review[3] and hence need not be discussed here in detail.

It has long been known, furthermore, that, in rats, certain steroids of the vitamin-D group can produce cardiac necroses with calcification.[4,5] The question now arose as to whether the latter change could also be influenced by excessive dietary phosphate. Normally, dihydrotachysterol (DHT) produces calcification and necrosis of the cardiac muscle, but no inflammatory reaction; however, simultaneous treatment with NaH_2PO_4 transforms the character of these lesions, so that a suppurative, acute myocarditis results.[6] Oral administration of either KCl or $MgCl_2$ prevents the development of the infarctoid cardiopathy that otherwise occurs following treatment with Me-Cl-COL plus NaH_2PO_4,[7] and it has been demonstrated more recently that orally administered KCl is also effective in preventing the myocarditis normally produced by combined treatment with DHT and NaH_2PO_4.[8]

It is the object of this communication to report upon experiments which show: first, that KCl prevents not only the myocarditis but also the Mönckeberg type of arteriosclerosis and the nephrocalcinosis that develop in rats treated with NaH_2PO_4 and DHT; and second, that $MgCl_2$ is also highly effective in both these respects.

From the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, Montreal, Canada.

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Fig. 1.

Fig. 2.

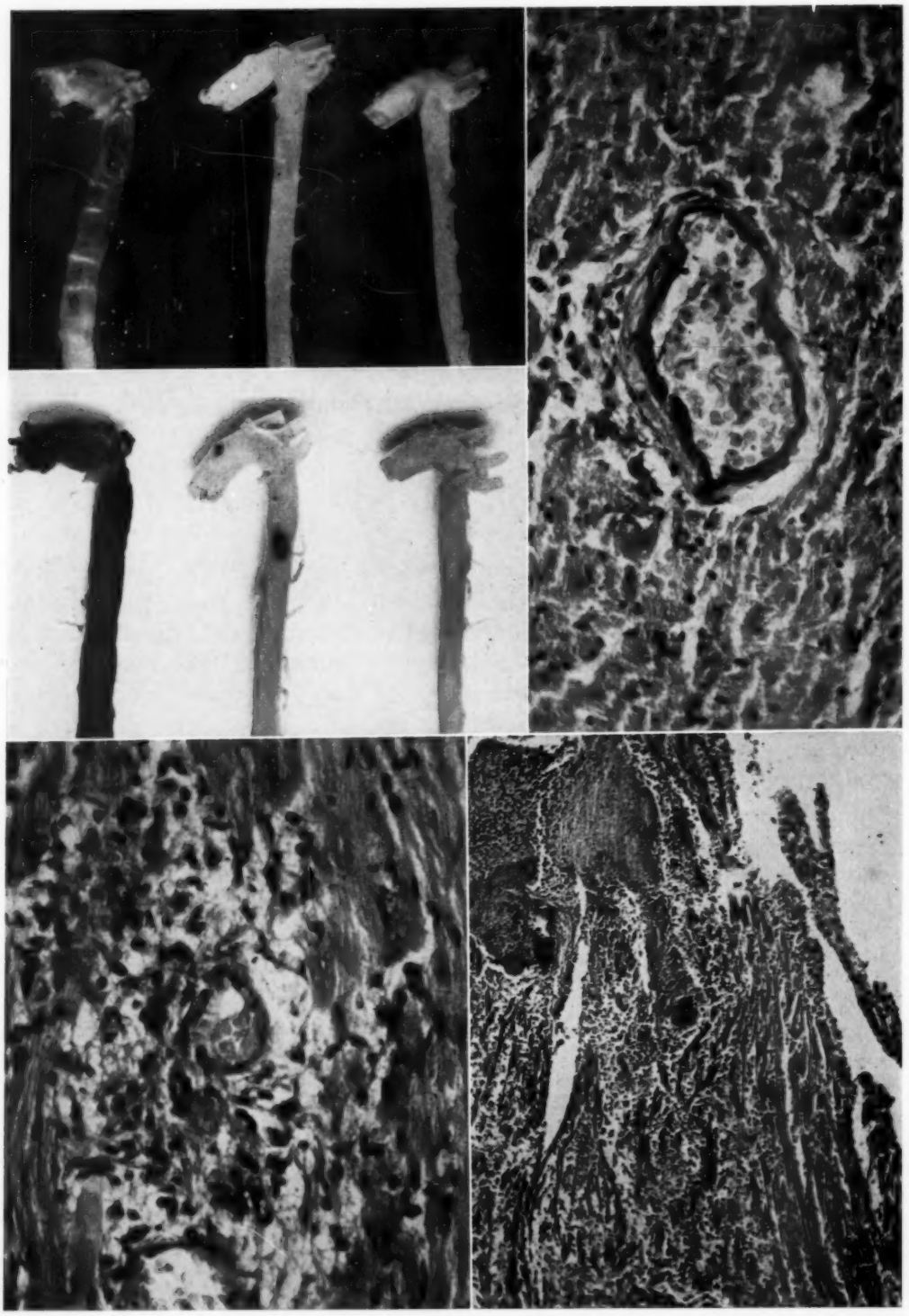

Fig. 3.

Fig. 4.

Figs. 1-4.—*(For legend see opposite page.)*

METHODS

One hundred-twenty female Sprague-Dawley rats, with an average initial body weight of 97 grams (range: 90 to 105 grams), were subdivided into 6 equal groups and treated as indicated in Table I.

Dihydrotachysterol (DHT) was administered by stomach tube, once daily, in the form of a microcrystal suspension, containing 40 μg in 0.5 ml. of water.

Monosodium phosphate ($NaH_2PO_4.H_2O$), magnesium chloride ($MgCl_2.6H_2O$), and potassium chloride (KCl) were each administered at the dose of 200 mg. in 4 ml. of water, twice daily, by stomach tube. Whenever two of these salts were given simultaneously, the two doses were dissolved together in 4 ml. of water, so as to maintain the volume of the solvent equal in all groups.

Treatment with all the electrolyte solutions was commenced 4 days prior to the initiation of DHT administration, in order first to permit some degree of adaptation to these salts. NaH_2PO_4 and $MgCl_2$ were very well tolerated, both when given alone and in combination. Among the rats receiving NaH_2PO_4 in combination with KCl there were no fatalities, but 6 of the animals treated with KCl alone died during the first 2 days. These were replaced, so that we still had 20 rats per group on the fourth day, when the DHT treatment was begun. Why NaH_2PO_4 protects against acute potassium intoxication is not known, but we have since confirmed the fact in several additional experimental series. It should also be mentioned that after several days of treatment with KCl alone, an initially toxic dose is usually well tolerated.

Throughout the period of observation the animals were kept exclusively on the laboratory food, Purina Fox Chow*, and tap water.

The experiment was terminated by killing all surviving rats with chloroform on the fourteenth day of the experiment, that is, after 10 days of DHT treatment.

TABLE I. PREVENTION OF DHT-INTOXICATION BY $MgCl_2$ AND KCl

GROUP	TREATMENT†	SEVERITY OF LESIONS (SCALE: 0 TO 3)			MORTALITY (%)
		HEART	AORTA	KIDNEY	
I	None	0	0	0	0
II	NaH_2PO_4	1.9 ± 0.2	2.2 ± 0.14	3.0 ± 0	60
III	$MgCl_2$	0.2 ± 0.1	0	0.3 ± 0.25	10
IV	NaH_2PO_4 + $MgCl_2$	0	0	0.8 ± 0.14	0
V	KCl	0	0	0.1 ± 0.1	20
VI	NaH_2PO_4 + KCl	0.3 ± 0.2	0.1 ± 0.1	2.0 ± 0.2	10

†In addition to the treatments listed in this column the animals of all groups received 40 μg per day of DHT, as indicated in the text.

*Ralston Purina Company, St. Louis, Mo.

Fig. 1.—Macroscopical appearance of the aortae of 3 rats which, in addition to DHT, received NaH_2PO_4 (left), NaH_2PO_4 plus KCl (middle), or NaH_2PO_4 plus $MgCl_2$ (right). The top picture shows these aortae in the natural state and demonstrates the widening and rigidity of the vessel on the left, with several calcified circular rings, in comparison with the smooth, supple aortae of the other 2 rats. In the bottom picture, the same aortae are photographed after histochemical demonstration of calcification with von Kossa's silver nitrate technique. The entire left vessel is calcified (now black), that in the middle shows only two calcified spots (which had not been detectable prior to staining), and that on the right is completely devoid of calcification.

Fig. 2.—Calcified coronary artery in a rat treated with DHT plus phosphate. (Magnification × 350; reduced 1/9.)

Fig. 3.—Arteritis and periarteritis in a noncalcified coronary artery of a rat treated with DHT and phosphate. (Magnification × 350; reduced 1/9.)

Fig. 4.—Necrosis of papillary muscles with a large, adherent, mural thrombus near the tip of the left ventricle of a rat treated with DHT and NaH_2PO_4. (Magnification × 75; reduced 1/9.)

Immediately after autopsy, the hearts, aortae, and kidneys were fixed in neutral Formalin for the subsequent histochemical demonstration of calcium with von Kossa's silver nitrate technique on slides lightly counterstained with hematoxylin-eosin. The severity of the lesions was appraised in terms of an arbitrary scale of 0 to 3. The means of these readings, with their standard errors, are listed in Table I. Only in the 3 animals used for the macroscopical illustration of the aortal sclerosis (Fig. 1) did we deviate from this procedure: in these the aortae were first photographed in their natural state and then again, after the entire Formalin-fixed specimens were stained with silver nitrate, for the macroscopic demonstration of calcium deposits.

RESULTS

Our principal findings are summarized in Table I.

Perusal of our data shows that the small dose of DHT used in these experiments did not suffice to produce any detectable lesion in the heart, aorta, or kidney (Group I).

On the other hand, following sensitization with NaH_2PO_4, marked lesions were noted in all of these organs (Group II). The aortae of all animals showed widespread calcification, often in the form of horizontal rings ("gooseneck aorta"), but no inflammation or edema (Fig. 1). In the heart there was calcification of the Mönckeberg type in the coronary vessels (Fig. 2), as well as edema and inflammation around the arteries (Fig. 3). There were also many foci of myocardial necroses and, in those cases in which these happened to occur just under the endocardium, occasionally, fresh thrombi developed in contact with the necrotic tissue (Fig. 4).

The kidneys of the rats in this group showed widespread calcification of the basement membranes around the convoluted tubules, and calcified casts, especially at the corticomedullary junction line.

Interestingly, both the cardiac changes and the calcification of the aorta were completely prevented by $MgCl_2$ (Group IV) and almost completely by KCl (Group VI). The nephrocalcinosis was less markedly, but still highly significantly, inhibited by $MgCl_2$, but only slightly reduced by KCl.

Although none of the animals treated exclusively with DHT succumbed (Group I), there was a 60 per cent mortality among those given DHT in combination with NaH_2PO_4 (Group II), and the survivors were virtually moribund when the experiment was terminated. On the other hand, the rats which, in addition to DHT and NaH_2PO_4, received $MgCl_2$ (Group IV) or KCl (Group VI), all survived, with the exception of 2 rats in the last-mentioned group which apparently died from KCl intoxication, as they showed no evidence of cardiac, aortal, or renal changes. The very low mortality among the animals treated with DHT and $MgCl_2$ (Group III), or DHT and KCl (Group V), must likewise be ascribed to some toxic effects of the electrolytes rather than to morbid changes induced by DHT poisoning, since they also revealed no lesions in the cardiovascular system or kidneys.

SUMMARY

The particularly intense arteriosclerosis of the Mönckeberg type, the cardiac changes, and the nephrocalcinosis that are normally elicited by comparatively

small doses of DHT, in rats sensitized with monosodium phosphate, can be inhibited by the concurrent administration of magnesium chloride or potassium chloride.

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REFERENCES

1. Selye, H.: Discussion, Laurentian Hormone Conference, Mont-Tremblant, Sept. 1-6, 1957.
2. Selye, H., and Renaud, S.: Proc. Soc. Exper. Biol. & Med. **96**:512, 1957.
3. Selye, H.: The Humoral Production of Cardiac Infarcts. Brit. M. J. (In press.)
4. Selye, H.: (Verein deutscher Ärzte in Prag, 26 Oktober) Med. Klin. **25**:167, 1928.
5. Selye, H.: Krankheitsforsch. **7**:289, 1929.
6. Selye, H.: Am. Heart J. **55**:1, 1958.
7. Selye, H.: On the Site of Interaction Between NaH_2PO_4 and $MgCl_2$ or KCl in the Prevention of "Phosphate-Steroid-Cardiopathy." Acta endocrinol. (Copenhagen). (In press.)
8. Selye, H., and Renaud, S.: Presse méd. **66**:99, 1958.

Estimation of Cardiac Output in Man by Dye Dilution Method Using an Automatic Computing Oximeter

P. Sekelj, Ph.D. Eng., D. V. Bates, M.D., A. L. Johnson, M.D., and W. Jegier, M.D., Montreal, Canada*

In a previous paper[1] we have described a method and an apparatus for continuous, quantitative estimation of the arterial concentration of Evans blue T-1824 dye. In this method the information obtained during the recording of dye dilution curves, as registered from the ear by means of a photoelectric earpiece, is automatically processed by an electronic computer. As judged by the close correlation which was found to exist between the values computed automatically and those calculated from the separate tracings obtained with the red and infrared filtered photocells, respectively, the performance of the computing system appears to be satisfactory.

In order to determine whether cardiac output studies utilizing this method could be made with sufficient accuracy, and without the necessity of standardizing each individual dye dilution curve against values of the plasma dye concentration determined photometrically, experiments were carried out in normal subjects and in a group of patients with cardiovascular anomalies, excluding intracardiac shunts. In the first set of experiments in the normal subjects the cardiac output estimations based on automatically computed dye concentration values were compared with those obtained by point-by-point calculations from the individual information recorded in each absorption band. In the second set of experiments the cardiac outputs obtained by the dye dilution method, using the computer, were compared with those obtained by the direct Fick procedure during cardiac catheterization.

MATERIAL AND METHODS

Dye dilution curves were recorded in 16 normal subjects by the technique described previously.[1] The subjects were adults of both sexes, aged 24 to 52 years, in 3 of whom the experiments were repeated on two different occasions. In the first 6 subjects radiant heat from the earpiece light bulb alone was used to produce vasodilation in the ear. In the others, Trafuril†

From the Department of Physiology, McGill University, and the Department of Cardiology, The Montreal Children's Hospital, Montreal, Canada.

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*From the University Clinic, The Royal Victoria Hospital, Montreal.

†Kindly supplied by the Ciba Company, Ltd., Montreal, Canada.

was lightly rubbed into the skin of the ear about 20 minutes prior to attaching the earpiece. Application of this vasodilator shortens the stabilization period and a steady base line is ordinarily obtained within a few minutes. During a period of about 30 minutes, while the instrument was warming up and the controls were being set, the subjects were allowed to rest. Then, measured quantities of 0.5 per cent T-1824 were rapidly injected into the antecubital vein, followed immediately by a rapid injection of 5 to 10 c.c. of physiologic saline.

The cardiac output was calculated from the following expression:

$$\text{C.O. (Blood)} = \frac{I \times 60}{k.A.H.} \text{ L./min.} \tag{1a}$$

where: I is the amount of injected dye in milligrams.

A is the area obtained from semilogarithmic replot by arithmetic summation of all concentrations from appearance time to the point where the extrapolated downslope from the point of maximum concentration intersects the time axis.

$H = \left(1 - 0.95\frac{Ht}{100}\right)$, is the hematocrit value determined from venous blood samples withdrawn before injection of dye, centrifuged for 30 minutes at 3,000 r.p.m. Five per cent was deducted from the hematocrit value to account for "trapped" plasma.

k is a constant.

The cardiac index was obtained from:

$$\text{C.I.} = \frac{I \times 60}{k.A.H.S.} \text{ L./min./M.}^2 \tag{1b}$$

where: S is the body surface area in square meter.

The determination of the constant, k, presented certain difficulties. It will be noted that the estimation of cardiac output by this method is based on the assumption that the calibrating line relating the deflections of the computer recording galvanometer to the plasma dye concentration is valid for all subjects. From the outset of this series of experiments it was observed that the values of cardiac index calculated from Equation 1b, with k = 1, were higher than normally accepted. Therefore, it appeared to be necessary to establish the constant, k, empirically. It could have been obtained on the basis of comparison between the values of cardiac output determined by this method and those estimated by the direct Fick or the Hamilton method. The procedure to employ the Fick method for the purpose of calibration, involving catheterization of the right heart in normal subjects, could not be considered. In addition, one of the main purposes of the present study consisted in an attempt to obtain sufficiently accurate estimates of cardiac output from the ear oximeter curves without the necessity of calibrating the instrument for each subject by collection and analysis of individual or serial samples of arterial blood. For these reasons an indirect method to determine the constant, k, was adopted. This consisted in: (1) introducing into Equation 1b the means of the data obtained in 3 groups of 5 subjects and in 1 group of 4 subjects (8 to 10 experiments in each group taken in chronological order in Table I); (2) equating Equation 1b with an acceptable value of cardiac index for normal subjects; (3) solving this expression for k.

The standard value of cardiac index was taken to be equal to 3.15 L./min./M.^{2}. This value represents the average of the means, based on the Fick procedure, of 3.18 L./min./M.^{2} and 3.12 L./min./M.^{2}, obtained by Stead and associates[2] and Cournand and associates,[3] respectively. Using this value of 3.15 L./min./M.^{2}, the calculated values for k in the 4 groups were: 1.241, 1.367, 1.261, and 1.228, respectively. Based on the means of the data obtained in 33 experiments (with the numerical values as follows: I = 0.21 mg./Kg. × 68.5 Kg. = 14.385 mg.; Ht = 40.6 per cent; A = 199.07 mg./L. × sec.; and S = 1.76 M.^{2}), the value of k was found to be equal to 1.274, the standard deviation of the differences being 0.063.

The similarity between the mean values of k obtained in the individual groups and the total mean suggests that a systematic relationship exists between the cardiac outputs determined by this method and those based on the Fick principle.

TABLE I

EXPERIMENT NO.	SUBJECT	SEX	PCV (%)	INJECTION	A.T. (SEC.)	B.T. (SEC.)	D.T. (SEC.)	CARDIAC OUTPUT (L./MIN.)		CARDIAC INDEX (L./MIN./M.²)	
								CALCULATED	COMPUTED	CALCULATED	COMPUTED
1.	A.D. (Indian)	M	48	1st	8	9	37	5.38	5.83	2.89	3.04
2.	W.J.	F	33	1st	13	6	17	5.71	5.89	3.52	3.63
3.	S.F.	F	37	1st	14	11	37	4.99	4.72	3.28	3.10
				2nd	14	10	35	4.13	4.22	2.71	2.77
4.	B.W. (Chinese)	M	45	1st	14	10	18	6.00	5.80	3.61	3.50
				2nd	13	9	19	5.57	6.12	3.40	3.68
5.	W.M.	M	42	2nd	13	12	20	5.99	6.04	3.35	3.39
6.	S.F.	F	34	1st	16	12	34	3.11	3.26	2.04	2.15
				2nd	13	12	38	3.48	3.78	2.29	2.48
				3rd	14	11	31	3.75	4.04	2.47	2.65
7.	G.R.	M	43	1st	14	12	34	4.03	4.54	2.35	2.65
8.	C.F.	M	43	1st	15	10	38	8.43	8.31	4.17	4.11
9.	A.D. (Indian)	M	44	1st	10	8	16	9.73	9.91	5.09	5.19
				2nd	12	9	18	9.66	9.36	5.05	4.89
10.	M.P.	F	37	1st	15	12	39	3.61	3.56	2.26	2.22
				2nd	12	11	27	3.57	4.06	2.23	2.54
11.	M.W.	M	42	1st	14	10	22	4.28	4.39	2.20	2.27

12.	R.P.	F	41	1st	11	7	15	6.53	7.40	3.28	3.72
				2nd	10	9	16	8.01	7.66	4.04	3.87
				3rd	11	10	21	6.92	6.72	3.49	3.39
13.	A.F.	F	36	1st	13	17	39	3.86	3.93	2.40	2.44
				2nd	13	17	38	3.94	4.17	2.44	2.59
14.	M.W.	M	40	1st	13	12	38	4.44	4.45	2.29	2.29
15.	P.J.	M	44	1st	11	8	22	6.31	6.18	3.31	3.25
				2nd	11	8	23	6.48	6.14	3.41	3.24
16.	R.O.	M	42	1st	12	8	29	4.70	4.89	2.58	3.23
				2nd	13	11	28	4.54	4.60	2.50	2.53
17.	J.Y.	F	41	1st	13	7	19	4.39	4.77	2.91	3.16
				2nd	13	8	27	4.24	4.46	2.80	2.94
18.	E.S.	F	37	1st	17	12	33	4.49	4.39	2.77	2.72
				2nd	16	10	32	4.75	4.70	2.93	2.91
19.	P.S.	M	42	1st	18	7	21	7.48	7.25	3.90	3.77
				2nd	17	8	22	6.72	7.10	3.51	3.69
Mean			40.6		13.2	10.2	27.36	5.43	5.53	3.07	3.15
Twice S.E. of the Mean			±0.9		±0.09	±0.025	±1.31	±0.30	±0.29	±0.14	±0.13
Range			33–48		8–18	6–17	15–38	3.11–9.75	3.27–9.91	2.05–5.09	2.15–5.19

A.T.: Appearance time. B.T.: Build-up time. D.T.: Disappearance time. (Determined from the semilogarithmic replot.)

Following these studies in normal subjects, 28 nearly simultaneous determinations by the Fick and the dye methods were carried out during routine cardiac catheterization in a second series of 12 patients with various pulmonary and/or cardiac anomalies, excluding intracardiac shunts. In 2 of these subjects the experiments were repeated on two different occasions. Nine of the subjects were children, aged from 3 to 9 years. They were, normally, given a combination of Demerol and Nembutal, 2 mg./Kg. of each, intramuscularly. All measurements were done with the subjects breathing room air, and a vasodilator, Trafuril, was used, as indicated previously, in all instances. First, the Fick procedure was carried out in the usual manner; then, 3 minutes after the commencement of the gas collection, a measured amount of 0.5 per cent solution of T-1824 was quickly injected through a cardiac catheter (Nos. 5 to 7) into the pulmonary artery or the right ventricle, followed immediately by a rapid injection of physiologic saline.

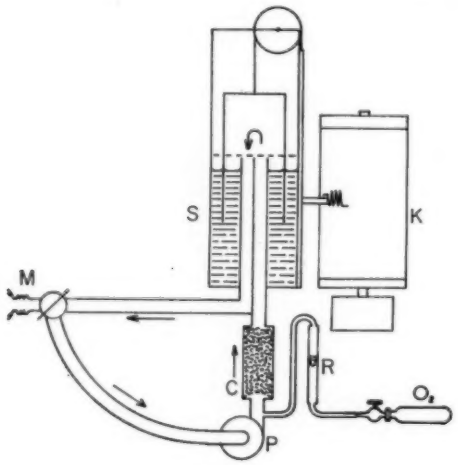


Fig. 1.—Circuit diagram of a closed-circuit apparatus for oxygen uptake. *S* = Small-sized spirometer. *M* = Mouthpiece. *P* = Pump. *R* = Sensitive rotameter. *K* = Kymograph.

The accurate measurement of oxygen uptake in small children during cardiac catheterization presents certain difficulties not normally present in respiratory studies. The collection of expired gas over a timed interval, and its subsequent analysis for O_2 and CO_2 content, is probably the simplest method to use. However, in practice it suffers from four disadvantages: (1) No respiratory record is obtained during gas collection; hence, the constancy of minute volume and oxygen uptake during blood sample collection are not known. (2) It is difficult to be sure that the collection starts and ends at the same phase of respiration. (3) In small children, heavily sedated, the respiratory minute volume may be insufficient to open and close the rubber-flap valves in the mouthpiece. (4) Since there is no spirometer in the circuit, leakage either around a mask or a mouthpiece is difficult to detect. The conventional basal metabolic rate circuit is unsatisfactory because the adult-size spirometer is too big and, hence, insensitive, and because the valve difficulty is still present.

These problems appear to have been satisfactorily overcome by the use of a closed circuit of small internal volume, with an oxygen inlet through a sensitive rotameter. The circuit diagram is shown in Fig. 1. The total circuit volume is 2.86 liters, and the spirometer has a "bell factor" of 8.5 ml./mm.; hence a 100-ml. change of volume moves the pen on the kymograph through 11.75 mm. The flow of oxygen is controlled by a sensitive needle valve and monitored through a small rotameter. On this, the rate of flow can be measured to within 5 c.c. per minute. The circuit is constructed so that the pressure at the mouthpiece is atmospheric.

The circuit was flushed with room air before use. The patient was attached to the apparatus either by a flexible rubber mouthpiece and nose clip or a face mask. The oxygen flow was then adjusted so that the respiratory tracing was level. By observation of the kymograph record any

leakage of the mouthpiece can be detected, and the constancy of ventilation and oxygen uptake observed. When both of the latter were steady, blood samples were withdrawn simultaneously from the pulmonary and brachial arteries, the rate of oxygen uptake being read at the same time on the rotameter.

RESULTS

The experiments performed in normal subjects served two main purposes: (1) to determine the calibrating constant, and (2) to evaluate the accuracy of the automatic computation. The procedure to establish the constant k = 1.274 was outlined earlier. This value of k was employed in all cardiac output determinations reported in this study. Table I shows the comparison between the estimates based on automatic computation and those obtained by point-by-point calculation. With an average dose of dye of 0.21 mg. per kilogram of body weight the values of cardiac output, using the computer, are 5.53 ± 0.24 (3.29 – 9.91) L./min., as compared with 5.43 ± 0.30 (3.11 – 9.75) L./min. by calculations. The numbers following the ± signs are the standard errors of the mean, and the numbers in parentheses indicate the range. The correlation is 0.988, and the standard deviation of the differences is 0.31 L./min.

The cardiac index values shown in Table I are, with the exception of Experiment 9,* in the range of 2.15 to 4.11 L./min./M.^{2}. It is interesting to compare these values with those reported by others for recumbent, resting normal subjects: Stead and associates,[2] by the Fick procedure, 2.40 to 3.09 L./min./M.^{2}; Cournand and associates,[3] by the Fick procedure, 2.12 to 4.01 L./min./M.^{2}; and Nicholson and Wood,[4] using the cuvette oximeter, 1.96 to 4.32 L./min./M.^{2}.

The experimental data and the comparison between the cardiac output measured by the Fick and the dye methods are shown in Table II. Fig. 2 is the graphic illustration of the correlation between the estimates based on both methods. With the subjects' ages varying from 3 to 55 years, the hematocrit values from 32 to 50 per cent, and the arterial oxygen saturations from 71.6 to 100 per cent, the cardiac output estimates by the Fick procedure are 3.83 ± 0.42 (0.90 – 9.84) L./min., as compared with 4.01 ± 0.46 (0.57 – 8.47) L./min. by the dye method. The correlation is 0.743, and the standard deviation of the differences is 0.88 L./min. It will be noted that the data pertaining to Subject E.S. (Table II, Experiment 5) are excluded from the statistical analysis, because the Fick values appear to be doubtful. While the A-V difference remained practically unchanged during the two successive determinations and the cardiac output was duplicated by the dye method within 1 per cent, the oxygen uptake varied by about 32 per cent. Both measurements by the Fick method show an abnormally low cardiac index for this subject. Disregarding these two experiments,

*The high cardiac index values of 5.19 and 4.89 L./min./M.^{2} found in Experiment 9 are due either to a technical error or, more likely, to the condition of the subject, who, with a heart rate of 85/min., might have had an elevated metabolic rate. On a separate date, 6 months earlier, the cardiac index in the same subject (Table I, Experiment 1) was 3.04 L./min./M.^{2}, with a heart rate of 70/min. In another subject measurements were made on two different occasions, 6 months apart (Table I, Experiments 3 and 6), which gave values of 2.93 and 2.42 L./min./M.^{2}, the heart rate being 72/min. in both instances. In still another subject two measurements were performed 3 months apart (Table I, Experiments 11 and 14), with the results of 2.27 and 2.29 L./min./M.^{2}, for heart rates of 63 and 66/min., respectively.

about 80 per cent of all determinations are within ± 25 per cent of the line of identity. The value of the dye method varied from +30 per cent to −51 per cent of the Fick value without apparent systematic difference.

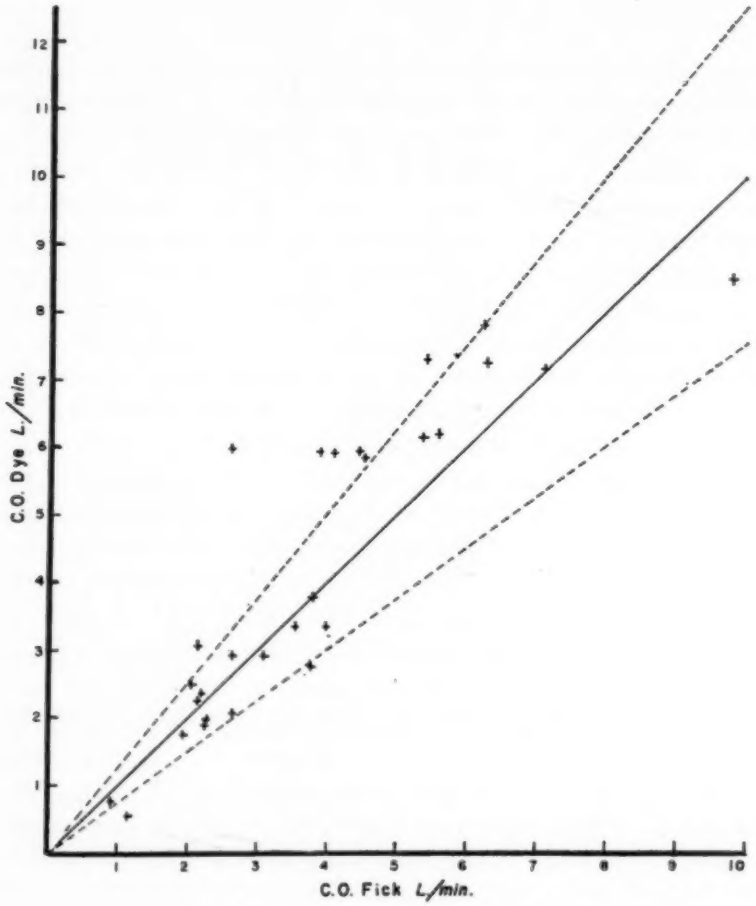


Fig. 2.—Relationship of cardiac output values determined by the Fick procedure and by the dye method, using the computing ear oximeter.

The greatest difference between the results of simultaneous determinations was found in Subject M.M. (Table II, Experiment 8), with an extremely low cardiac output of 1.16 and 0.90 L./min. by the Fick method, and 0.57 and 0.78 L./min. by the dye method. Because of the inherent variability of both methods, errors of this magnitude may be expected to occur in the very low range of cardiac output.

The correlation between duplicate estimates by the dye method, obtained in 26 subjects, is shown in Fig. 3. Not considering the experiments in which both the Fick and the dye methods recorded changes exceeding 15 per cent occurring in the same sense, 21 out of 24 duplicates are within ± 15 per cent, and all of them are within ± 20 per cent of the line of correlation. The standard deviation of the differences of the duplicate estimates is 0.37 L./min.

With regard to the accuracy of the oxygen uptake measurements, it is noted that an insufficient number of patients have been studied to enable a vigorous statistical comparison to be made between duplicate measurements using the circuit described earlier and those using a Douglas bag. In 6 of the patients in Table II (8, 9, 10, 12, 13, and 14) the closed circuit method was used,

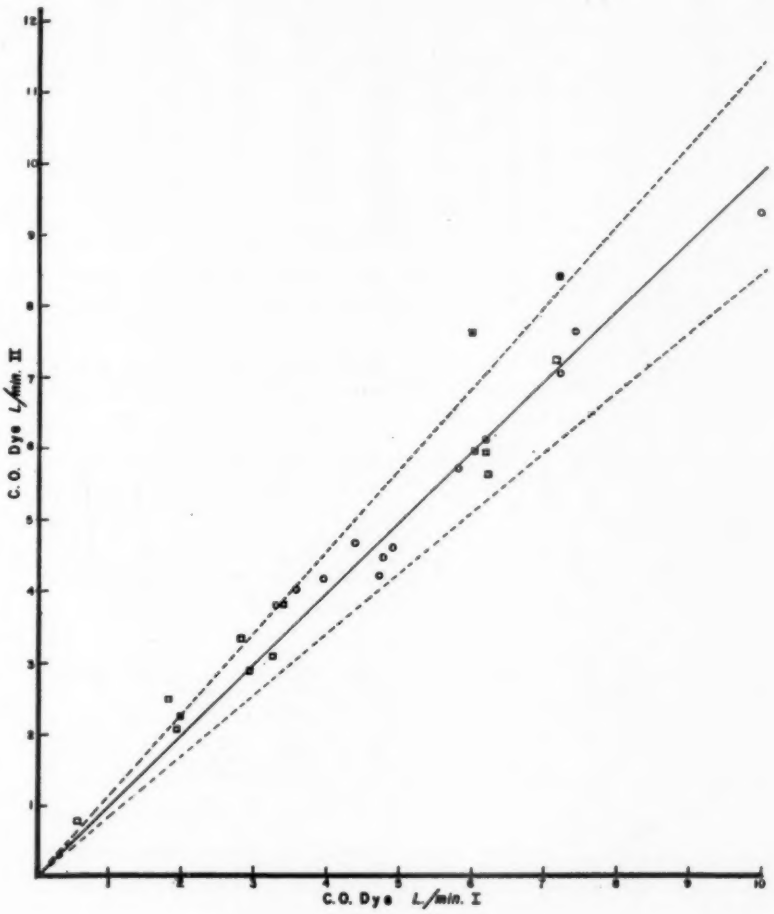


Fig. 3.—Relationship between two successive cardiac output estimates obtained by the dye method. The circles refer to normal subjects, the white squares to subjects with cardiac and/or pulmonary anomalies, the black squares to cases in this latter group in which both the Fick and dye methods recorded changes exceeding 15 per cent occurring in the same sense.

and the average difference between the two estimates of oxygen uptake in this group is 13 ml. In the remainder, expired gas was collected and analyzed with the Scholander apparatus. Technical errors during gas collection were suspected in 2 of these patients, and the average difference between the two estimates of oxygen uptake in this series is 29 ml. Subsequent experience with the closed circuit has confirmed its value, particularly in children with low minute volume.

TABLE II

EXPERIMENT NO.	SUBJECT	AGE (YR.)	SEX	HEMATOCRIT (%)	INJECTION (MG./KG.)	ARTERIAL O_2 SAT. (VOL. %)	A-V (VOL. %)	O_2 UPTAKE (C.C./MIN.)	CARDIAC OUTPUT (L./MIN.)		CARDIAC INDEX (L./MIN./M.^{2})		DIAGNOSIS
									FICK	DYE	FICK	DYE	
1.	R.C.	13	M	42	0.213 0.270	94.0 98.0	4.65 5.03	163 190	3.52 3.78	3.37 3.76	2.41 2.60	2.35 2.61	Pulmonic stenosis, severe with a gradient of 150 mm. Hg across pulmonary valve
2.	R.G.	7½	M	36	0.206 0.352	94.6 95.4	4.78 5.15	106 111	2.23 2.16	2.36 3.08	3.17 3.08	3.36 4.39	Valvular pulmonic stenosis, gradient of 50 mm. Hg
3.	A.F.	3½	M	32	0.218 0.213	92.6 89.4	4.99 5.12	114 110	2.28 2.15	1.96 2.26	3.40 3.21	2.81 3.23	Valvular pulmonic stenosis, gradient of 150 mm. Hg preop.
4.	F.B.	16	F	40	0.225 0.212	100.0 99.5	3.90 3.80	159 230	4.08 6.21	5.94 7.82	2.55 3.91	3.73 4.92	Rheumatic heart disease with asymptomatic mitral stenosis
5.	E.S.	33	F	41	0.206 0.206	97.2 96.6	5.46 5.27	141 206	2.59 3.91	5.99 5.95	1.45 2.19	3.36 3.34	Valvular pulmonic stenosis, gradient of 175 mm. Hg preop.
6.	T.Z.	55	M	50	0.186 0.206	71.6 72.6	4.23 5.06	217 227	5.71 4.52	6.20 5.85	3.55 2.78	3.37 3.35	Chronic pulmonary disease, emphysema, cor pulmonale, and compensated congestive heart failure
7.	S.M.	6	F	39	0.205 0.303	89.0 90.3	3.14 3.11	82 96	2.63 3.09	2.92 2.94	3.12 3.68	3.45 3.47	Valvular pulmonic stenosis, gradient varying from 60 to 85 mm. Hg

8.	M.M.	3½	F	34	0.211 0.306	92.5 89.0	5.95 6.12	69 55	1.16 0.90	0.57 0.78	2.01 1.75	1.00 1.36	Primary pulmonary hypertension
9.	R.R.	17	M	48	0.207 0.201	95.6 93.6	3.49 2.80	253 285	7.13 9.84	7.17 8.47	4.02 5.56	4.05 4.79	Valvular pulmonic stenosis, gradient of 135 mm. Hg across pulmonary valve
10.	A.F.	3½	M	34	0.205 0.202	99.0 95.4	4.27 3.95	96 103	2.26 2.63	1.90 2.07	3.43 3.98	2.72 2.95	Postop. pulmonic stenosis, gradient of 30 mm. Hg
11.	E.S.	33	F	39	0.194 0.192	95.8 95.8	3.78 3.44	195 215	5.42 6.28	7.32 7.28	2.91 3.53	4.11 4.08	Valvular pulmonic stenosis, gradient of 35 mm. Hg
12.	R.F.	6	M	34	0.209 0.333	97.0 97.3	5.62 5.91	108 121	1.93 2.05	1.79 2.50	3.02 3.21	2.83 3.95	Congenital aortic stenosis
13.	L.M.	8½	F	35	0.316 0.202	75.5 90.0	4.40 4.29	165 171	3.76 3.98	2.79 3.36	3.75 3.98	2.79 3.36	Chronic rheumatic heart disease with marked cardiac enlargement; severe mitral insufficiency, pulmonary hypertension
14.	M.K.	34	F	36	0.215 0.188	92.8 95.5	3.35 3.92	179 179	5.37 4.48	6.16 5.96	3.60 3.00	4.13 4.01	Valvular pulmonic stenosis with a gradient of 85 mm. Hg across pulmonary valve
	Mean			38.57	0.228	92.34	4.46	155.60	3.83	4.01	3.27	3.35	
	S.E. of Mean			±2.76	±0.016	±2.77	±0.35	±10.10	±0.42	±0.46	±0.15	±0.17	
	Range			32-50	0.186-0.352	71.6-100.0	3.11-6.12	55-285	0.90-9.84	0.57-8.47	1.75-5.56	1.0-4.79	

COMMENTS

The assumption, that the principles upon which the operation of the oximeter for determination of the absolute value of the arterial oxygen saturation is based may be applied to quantitative estimation of the arterial dye concentration, appears to be substantiated by the results obtained. The method simplifies the measurement of cardiac output in man by avoiding the necessity of difficult and time-consuming calibration for each individual dye dilution curve. This advantage does not appear to be offset by an increase in the variability of the estimations, as evidenced by the satisfactory agreement obtained between the Fick and the dye values. Since no blood sample is required, discomfort to the patients is reduced, and the steady state is not disturbed. This consideration merits attention when multiple, successive measurements are required in small children and infants.

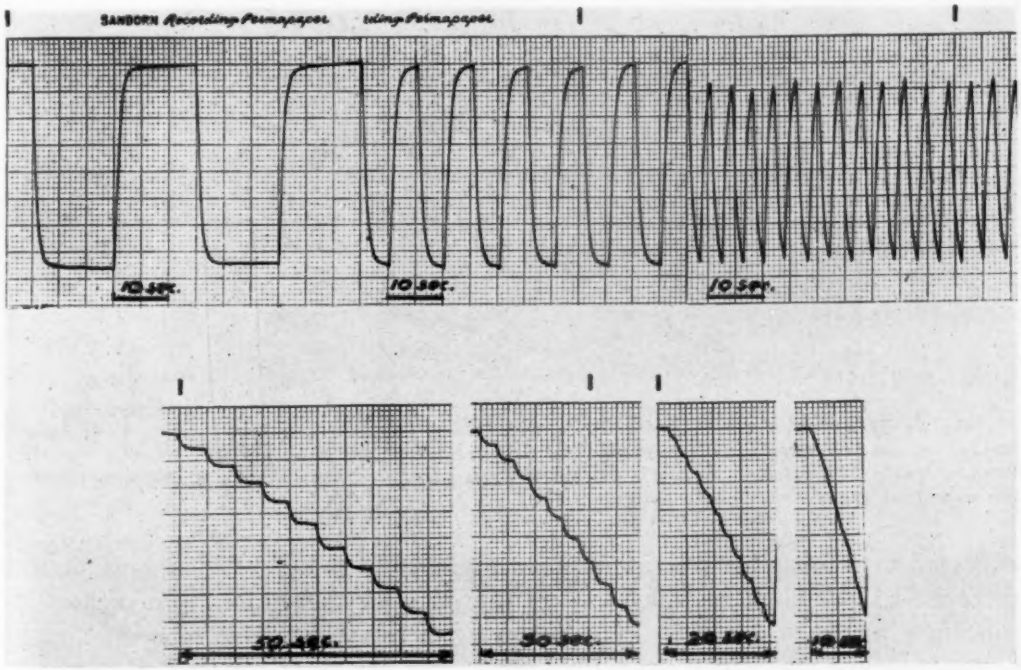
It is possible to estimate the cardiac output by using the earpiece and oximeter alone, without the computing system, by point-by-point calculations. This is, however, a time-consuming procedure, which consists, briefly, of introducing into Equation 1[1] the logarithms of the readings obtained in the red and infrared channels for each second during the primary curve, and reading off the corresponding values of the dye concentration from the calibration diagram. Great simplification would result by performing the calculations for one point only, preferably for the point of maximum concentration. This procedure, however, assumes a linear relationship over the whole practical range, between the dye concentrations and the instrument readings. Because the calibration line departs from linearity below about 4.0 mg./L., the error in the estimations will increase in proportion to the decrease in the amount of dye injected. The error may be reduced by injecting quantities of dye exceeding substantially the 0.2 to 0.3 mg./L. range used in these studies. This procedure may be objectionable in many instances, on esthetic grounds, when two or more successive determinations have to be carried out.

There is one aspect which deserves attention, and that is the one which is concerned with the empirically determined calibration constant. Granting that the calibration diagram is correct, it could be expected that the ratio of the average values of cardiac output measurements obtained by both the ear oximeter and the Fick method should be equal to 1, or reasonably close to it, within the limits of the accuracy of the methods. The results obtained in normal subjects, and in those with cardiac and/or pulmonary anomalies, show that with $k = 1$ the dye values averaged about 27 per cent higher than the Fick values. The reason for this apparent difference is not clear at present. Beard and Wood[5] reported that the values obtained by the ear oximeter, using the venous method of calibration, averaged 37 per cent greater than the determinations obtained with the cuvette oximeter. According to these workers the systematic error produced by the venous method of calibration was due, in part, to an apparent difference in the determined value for concentration of dye in samples of arterial and oxygenated venous blood. They found that the dye concentration in vitro was significantly lower in the oxygenated venous blood than in the untreated arterial blood. In our case the venous blood samples were not oxygenated; hence,

possible changes in the spectral transmission characteristics due to the in vitro oxygenation procedure did not affect the measurements. It is a matter of speculation whether the error may not arise, at least in part, from a possible difference in the hemoconcentration in the arterial blood and in the capillary blood of the heat-flushed ear.

A further source of error, apparently slight but not negligible, and one which is also accounted for in the calibrating factor, results from limitation in the dynamic response properties of the system. It will be recalled that the construction of the calibration line is based on measurements made under static conditions, 5 minutes after injection of the dye, when equilibrium in the dye concentration is assumed to exist between the arterial and venous systems. The concentration-time curve, however, represents a continuous measurement made

A.



B.

Fig. 4.—*A*, Recordings of the dynamic response of the system to stepwise changes in the photocell outputs. The pulses of 2, 6, and 15 cycles per minute simulate sudden changes in dye concentration from 0 to 16.5 mg./L. equivalent. They were produced by periodically opening and closing (manually) a micro switch across a resistance in series with the filament of the earpiece light bulb. The recordings were obtained with a standard filter inserted in the earpiece, simulating an average ear. It is noted that as the frequency of the variations increases, the amplitude of the response decreases gradually to about 98 per cent, at 6 cycles per minute, and to 90 per cent, at 15 cycles per minute, of the response at 2 cycles per minute. Ninety per cent of the maximum deflection is reached in 1.5 seconds, and at 2 cycles per minute there is no visible attenuation of the response. *B*, Recordings show the response to 10 successive stepwise changes, each equivalent to 1.65 mg. per liter of dye concentration. These were produced by sudden, stepwise increases in the resistance value in series with the light bulb, causing corresponding changes in the photocurrents to occur. Attenuation of the response is not observed when the stepwise changes occur in 5-second intervals. It becomes noticeable when the rate is increased to one step in 3 and in 2 seconds, respectively, and there is a definite decrease in the amplitude to about 92 per cent of the maximum response when the rate is one step per second. At this rate of change the inertia of the light source contributes greatly to the decrease in the amplitude.

under dynamic conditions, with the dye concentration varying rapidly in the blood. The error in estimating the area inscribed under the curve, due to amplitude and phase distortion, depends upon the dynamic response characteristics of the system. The recordings shown in Fig. 4,*A* and *B* illustrate the response of the system to stepwise changes in the output of the photocells, when a standard filter simulating an average ear is present in the light path. The response under normal operating conditions is probably different, but not significantly so, from that shown in the recordings. Variations in dye concentration which may be

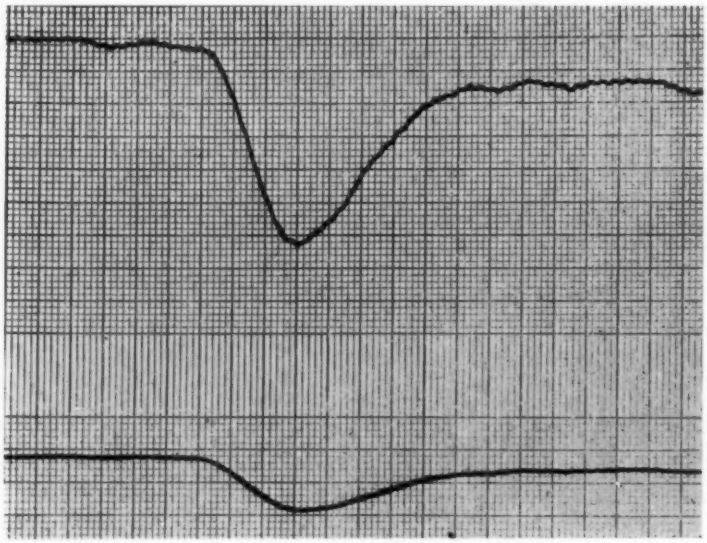


Fig. 5.—Dye dilution curves recorded in a normal Negro adult. The upper tracing was obtained by the computer recorder, the lower tracing with the "red" amplifier connected directly to the recorder. Both recorders were adjusted to have equal deflection sensitivity. Note the striking difference between the deflection amplitudes of both tracings.

expected to occur in human circulation are seldom of the order of magnitude and of rate as those changes which caused the recorder deflections to decrease significantly in Fig. 4,*A* and *B*. The adequacy of the response to reproduce rapid changes in dye concentration with a reasonable degree of accuracy is apparent from the recordings shown. This is evidenced also by the satisfactory results obtained, in most cases, when recording dye dilution curves in children with abnormal circulatory pathways, elevated heart rate, and rapid fluctuations in dye concentration during the passage of the dye.

The deflections proportional to changes in optical density, when recording dye dilution curves from the ear by means of a photoelectric earpiece, are usually very small, and the curves may become unintelligible in the presence of a considerable background density due to a high degree of arterial unsaturation or deep pigmentation of the skin. It might be thought that this difficulty could be overcome by increasing considerably either the amount of the dye injected or the sensitivity of the amplifying system. Desirable as such procedures may be, they are impractical or extremely difficult to realize. This difficulty is, how-

ever, overcome by the use of the computer, because the results appear in terms of arterial dye concentration, and not in terms of optical density. The arterial dye concentration depends, mainly, on the amount of dye injected, the circulatory pathway, and the velocity and volume of the circulating blood, and should be independent of nonspecific factors, such as color of the skin, arterial oxygen saturation, etc.

The recordings shown in Fig. 5 illustrate this point. These were obtained in a normal Negro subject. The upper tracing refers to the output of the computer, the lower to that of the "red" amplifier connected directly to the recorder. The tracings were obtained with recorders of equal deflection sensitivity. The difference between the deflection amplitudes of these simultaneously recorded curves is striking.

SUMMARY

Estimation of cardiac output by the dye dilution method with an automatic computing oximeter is described. This instrument provides a quantitative and continuous measurement of the arterial concentration of Evans blue T-1824 dye, by performing a computation of the data obtained from the ear by means of a photoelectric earpiece.

This method has the obvious advantage of doing away with the necessity of collecting and analyzing blood samples for the purpose of calibrating individual dye dilution curves.

Other advantages of the method and the procedure to determine the instrument constant for cardiac output are discussed.

Studies in normal subjects show a close correlation between the cardiac output estimates based on the automatically computed dye concentration values and those obtained by calculation from the instrument readings.

Satisfactory agreement is found between the nearly simultaneous estimates obtained by the direct Fick procedure and by this method, using a single calibrating factor for all subjects.

The sensitivity and the dynamic response characteristics of the system appear to be adequate for several consecutive determinations of cardiac output when small quantities of dye (about 0.2 mg./Kg. per injection) are used.

We express our appreciation to the following members of The Montreal Children's Hospital staff: to Dr. M. McGregor for his helpful discussions, to Miss N. Corbeil, B.Sc., and Miss H. Tetrault, B.Sc., for their technical assistance, and to Miss A. Pratt for her secretarial assistance.

REFERENCES

1. Sekelj, P., Jegier, W., and Johnson, A. L.: Am. Heart J. **55**:485, 1958.
2. Stead, E. A., Jr., Warren, J. V., Merril, A. J., and Brannon, E. S.: J. Clin. Invest. **24**:326, 1945.
3. Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. deF., and Richards, D. W., Jr.: J. Clin. Invest. **24**:106, 1945.
4. Nicholson, J. W., III, and Wood, E. H.: J. Lab. & Clin. Med. **38**:588, 1951.
5. Beard, E. F., and Wood, E. H.: J. Appl. Physiol. **4**:277, 1951.

Notes on the Planning and Evaluation of Research, With Examples From Cardiovascular Investigations. Part II*

Donald Mainland, M.B., Ch.B., D.Sc., New York, N. Y.

V. INTERPRETATION OF RESULTS

V-1. *How shall we decide whether the results prove, or fail to prove, that the factors under test were responsible for the differences in outcome in the samples that were compared—(a) By inspection of the results in the light of our previous experience (e.g., experience of observational error, average level, and variability of animal responses)? (b) By a formal test of "statistical significance"?*

V-2. *If method (a) is to be used, what specifically (numerically) is the experience or background knowledge?*

Method (a) has been the customary method of assessment for generations, and no one can deny its value in the hands of a critical observer who has much experience of the particular material on which he is working. Nowadays, however, more and more experimenters are becoming dissatisfied with it. They are discovering that their background of knowledge is not so extensive, or so exact, or so pertinent to new material and conditions, as they had imagined. They have learned, also, how we can "make chance work for us" in our experiments (Question V-3).

V-3. *If method (b)—a formal test of "significance"—is proposed, and the investigation is an experiment, what precautions will be taken in order to make possible an inference of the form "either chance or the factors under test"?*

"For each of these three duration groups, within each age group, and separately for each treatment center, the three treatments, ACTH, cortisone and aspirin, were listed in random order for as many patients as were likely to be admitted, using random sampling numbers and keeping the numbers of patients on the three treatments approximately equal in each center. The coordinating center in each country issued serially numbered and sealed envelopes to the treatment centers. Thus, on admission of a patient of given age and specified duration-from-onset group, the investigator at the treatment center had merely to open the next available envelope for that particular group to find a statement of the treatment to be applied" (Rheumatic Fever Trial report,[1] p. 347).

From the Department of Medical Statistics and the Study Group on Rheumatic Diseases, New York University College of Medicine, 550 First Avenue, New York 16, N.Y.

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This kind of procedure, now familiar to many clinical investigators, is apparently often thought to be simply a device for avoiding conscious or unconscious psychological bias. It plays a far more fundamental role, which has nothing to do with sealed envelopes.

Residual Variation.—However much alike the Rheumatic Fever Trial investigators had made the three treatment groups with respect to age, duration of disease, cardiac condition, temperature, and a host of other features, even to the extent of utilizing uniovular triplets if they had been available, intersubject variation would always have remained. That is to say, there would have been factors, many of them unknown, in the patients when they arrived, and in events and environment during therapy, that would or might have made different patients respond differently to exactly the same therapy. This is the *residual variation*—the variation that remains within subclasses.

The investigators knew that at the end of the experiment they would wish to make proper allowance for this residual variation—to be able to make a statement such as the following: "When chance alone is operating, the differences in outcome that we have observed between the treatment groups happen very rarely—less than once in 20 [or 50, or 100] experiments. Therefore, we feel justified in attributing the differences in outcome to the differences between the treatments." They knew that the only way to attain this position was to make sure that nothing except the treatment differences and chance could be responsible; that therefore they must allocate treatments to patients (= patients to treatments) strictly by chance (strictly at random). In other words, they must employ randomization—an automatic process controlled by chance.

Randomization.—In a subsequent article it is intended to discuss randomization methods and results at some length. Here it will suffice to visualize the allocation of 30 patients, 10 each to ACTH, cortisone, and aspirin, by card shuffling, instead of the speedier equivalent method (random numbers) employed in the Rheumatic Fever Trial. We could number 30 playing cards 1 to 30, to indicate the order in which the patients would be admitted to the trial. We could shuffle the cards very thoroughly and finally mark the top 10 of the shuffled cards "ACTH," the next 10 "Cortisone," and the bottom 10 "Aspirin."

After the therapy we would, as usual, employ predetermined criteria of improvement, and classify patients—for example, as "successes" (S) and "failures" (F)—with respect to a certain sign or symptom or laboratory test. In our randomization, therefore, we can imagine that each of the 30 cards bears an invisible letter, S or F, indicating outcome—letters which, as it were, become visible after therapy. If there is no difference between the effects of the three treatments, our randomization will distribute the S's and F's by pure chance. Therefore, taking the actual numbers of S's and F's that emerge from the therapeutic trial, we could insert them on a set of 30 cards (one letter on each card) and find out experimentally (by, say, 1,000 shuffling experiments) how often they were divided among three groups of 10 as unequally as in the therapeutic trial itself.

If the distribution of F's and S's in the therapeutic trial were so disproportionate that they occurred in, say, fewer than 5 per cent of our 1,000 shuffling experiments, we would feel justified in concluding that the results of the trial

were probably due to something more than chance. Having kept out bias during the experiment by handling the three treatment groups uniformly except for the specific therapy, we could conclude that the difference was due to the treatments.

Testing Results After Randomization.—Actually, we do not need to perform the shuffling (randomization) experiment, because, from long experience of chance, including actual randomization experiments, we know what chance will do in such circumstances. This is the experience that justifies the use of the mathematical formula (the chi-square test) that we apply in order to test data in contingency tables. The validity of the chi-square and other statistical tests, applied to data in the real world, *does not rest on the mathematician's derivation ("proof") of the formula.*

In a practical (nonmetaphysical) sense we accept the evidence of a properly conducted experiment as proof of a causal relationship, under the specified conditions of our experiment. Such proof, unlike mathematical deduction, always has an error term or "estimate of uncertainty" attached to it, i.e., a statement of how often such causal inferences are made when, in actual fact, chance alone is the cause of the observed differences. That is what is meant by a statement such as "P (the probability) is less than 0.05, or 5 per cent." The word "probability," suggesting a guess, is unfortunate. We should equate it to "chance percentage frequency."

V-4. *If the investigation is a survey, or an experiment not conducted along the lines indicated under Question V-3, what would a test of "significance" tell us? Would it be helpful?*

Risk of Hidden Bias.—Here we come upon the vital distinction between a survey and a properly conducted experiment (Question I-3). In a survey we might, with sufficient subjects, make our test group alike with respect to all factors known or suspected to influence the occurrence or nonoccurrence of X, except the factors under test (A and B); but we should remember that factors previously hidden are continually being discovered—biochemical, physiologic, genetic, environmental, and psychologic factors associated with pathologic or other phenomena that we study. At any time, a factor now hidden may be discovered—for example, F, a factor so closely related to the phenomenon under study (X) that if we knew about it now, we should no more think of mixing F's and not-F's in our study sample than we think of mixing, say, children and adults. Indeed, there are likely to be many such factors. As has been remarked elsewhere,[2] causation in medicine is like an iceberg, mostly hidden from view, but we often behave as though what we can seen now is all that matters, and we disregard the submerged mass that may wreck our causal inferences.

In every experiment, of course, there is also a submerged mass of potential bias-causing factors; but by randomization we make chance control their effects. Thus, by adopting the 5 per cent level of significance, we insure that we shall not be led to a false causal inference in more than 5 per cent of experiments in which chance alone is responsible.

Interpretation After a Survey.—In a survey we have no protection against hidden bias. Therefore, our interpretation of results cannot take the simple "either-or" form. We have to consider three possible causes of the observed

differences: (1) chance, (2) the factors under test, and (3) hidden bias, not controlled by chance. A statistical test can tell us only that chance was an unlikely cause, perhaps extremely unlikely, with probability (P) infinitesimally small.

The greatest usefulness of statistical significance tests after a survey is to show us, by a verdict of "not significant," that what looks to us like a real association (or a big difference) often occurs when chance alone is operating. Such verdicts, even after a properly conducted experiment, never tell us that chance *was* the cause. They are simply verdicts of "not proven"; but they often help us to decide whether to drop our search.

If, however, a statistical test after a survey gives a verdict of "significant" or even "highly significant" (with a very low P value), we are in grave danger unless we know how little this verdict means. It eliminates only one of the three possible causes enumerated above, and we must choose between the other two possibilities without the help of arithmetic. Our bases of inference and action after a survey include: the credibility of our proposed causal interpretation, its potential usefulness, the existence of other evidence pointing in the same direction, the possible danger if we are mistaken, and our opportunities of putting our conclusions to the test of experience. The probability value derived from a statistical test is no measure of our possible error in such an inference. If we rule out chance when we meet a P value of one in a hundred, a P value of less than one in a million comes no nearer to proving that our causal interpretation is correct.

In brief, except after a properly conducted experiment, *proof of association is not proof of cause.* If we equate the two, we are in serious danger of the *post hoc ergo propter hoc* fallacy, known long ago by logicians. It is pathetic how many research workers still take data to a statistician, thinking that by arithmetic he can deliver them from this peril.

Experiments that are conducted without randomization are equivalent to surveys with respect to uncertainty of inference. When an investigator asks for a "statistical analysis" (i.e., a significance test) after such an experiment, he apparently believes that he has left nothing in his experiment except chance and the factors under test—that he has eliminated biases, or has made them so small that they are trivial in comparison with the difference that he is measuring. He may be perfectly right, but a statistical test does nothing to prove him right. As E. B. Wilson,[3] a Harvard professor of chemistry, has written, "fifty pages of higher mathematics will not salvage an experiment with a hidden bias." Elimination of chance as a likely cause of an observed difference is of no importance if we cannot answer the question: "What has really happened to the biases that are always present in any experiment?"

V-5. *If a significance test is to be applied, what does it mean in terms of an experiment conducted with chance? What assumptions underlie the test? What is the evidence that they are valid for our data?*

"Less than 1 per cent of research workers clearly apprehend the rationale of statistical techniques they commonly invoke." This statement was made by Lancelot Hogben,[4] the experimental biologist, who wrote the enlightening and

popular book *Mathematics for the Million*, and who is now a medical statistician. The percentage does not appear to be a gross underestimate to the present writer, after reading innumerable research reports, after trying to help investigators with statistical methods, after struggling with the writings of mathematical statisticians who produce the techniques, and after reading many of the statistics textbooks used by research workers.

It is intended that a future article shall discuss this matter. In the meantime two remarks may be made: (1) Many research workers would be astonished if they knew the hidden assumptions in some of the statistical tests that they take on trust, and if they realized how little evidence their data contains regarding the validity of those assumptions. (2) An investigator displays remarkable credulity, often unlike his other research behavior, if he performs (or requests, or demands) a statistical test without knowing its experimental equivalent, such as the thousand card-shufflings mentioned under Question V-3.

V-6. *If a "significance" test is to be applied, what level of significance will be adopted as the critical level? Why was it chosen?*

The rather misleading jargon in the first sentence means simply: "What value of P (the frequency of occurrence when chance alone is operating) shall we choose as our dividing line between two classes of observed differences: (1) those that we shall interpret as due to more than chance, and (2) those that will not convince us that anything more than chance was operating?" The choice rests with us, the investigators; but we must, of course, make the choice before we see the results. The standards $P = 0.05$ and, for greater confidence, $P = 0.01$ have been adopted by many investigators, but they are not laws of Nature, as some workers seem to think.

Two Types of Error.—The dividing line $P = 0.05$ insures that in no more than 5 per cent of our experiments in which chance alone is the cause of the observed differences shall we attribute these differences to the factors under test. But this is only one kind of error that we can make—often called a "Type I" error. We can also make the other kind of error. We can say that there is no significant difference between the effects of the factors under test when there is, in fact, a difference. In most research we cannot estimate our "Type II" error, but we know that if we make our Type I error low, by insisting that an observed difference must be so large that P is less than 0.01 (or less than 0.001), our risk of failing to detect a small but real difference will be greater than if we are satisfied with $P = 0.05$ as our Type I error.

Choice of "Significance Levels".—The choice of standard often depends on circumstance. For example, if treatment A appears better than treatment B, but P is only about 0.10 (a 10 per cent Type I error), we may be willing to accept, and act upon, the evidence in favor of A if that therapy has other advantages over B, such as lack of toxicity, cheapness, or ease in application.

On the other hand, if an experiment contradicts an apparently well-established belief, we are inclined to demand a higher standard than $P = 0.05$—perhaps even $P = 0.001$.

Finally, we should remember the words of one of the chief founders of experimenters' statistics, Sir Ronald Fisher[5]: "The 'one chance in a million' will

undoubtedly occur, with no less and no more than its appropriate frequency, however surprised we may be that it should occur to *us*. In order to assert that a natural phenomenon is experimentally demonstrable we need, not an isolated record, but a reliable method of procedure. In relation to the test of significance, we may say that a phenomenon is experimentally demonstrable when we know how to conduct an experiment which will rarely fail to give us a statistically significant result."

V-7. *What are the various possible outcomes of the investigation? What would be our action—our next step—in each case?*

By answering this question and the next one, we can help ourselves to decide, from our knowledge of what we may expect, whether the search will be profitable. To simplify and exaggerate, let us suppose that antihypertensive drugs, A and B, were compared in the same patients. Drug A reduced the diastolic blood pressure more than did drug B, by 3 mm. of mercury on the average, and this mean difference was significant (P less than 0.05). By contrast, let us suppose that the mean difference was 30 mm., with the same P value. The 3-mm. difference might be a useful clue for further development of antihypertensive compounds, but not in practical therapy, whereas the 30-mm. difference might prompt one to use A instead of B. *"Statistically significant" is not synonymous with "important for our purposes."*

V-8. *How shall we estimate what our results really tell us, numerically, about the population represented by our samples?*

The Rheumatic Fever Trial report gives the following information regarding children who had chorea at the start of therapy:

TREATMENT GROUP	NUMBER WITH CHOREA AT START OF THERAPY	NUMBER WITH CHOREA AT END OF THERAPY
ACTH	9	1
Cortisone	19	2
Aspirin	26	9
Total	54	12

Although chorea persisted in a higher proportion of the aspirin-treated children than of the others, the intertreatment differences are not significant at the 5 per cent level (P from chi-square is between 0.2 and 0.1). For all that we can tell, larger samples might actually show a higher frequency of persistent chorea in one or both of the hormone-treated groups.

However, a significance test answers only one kind of question. It may be equally, or more, important to ask the following kind of question: "If, in reality, the three treatments do not differ in their effects on the persistence of chorea, what does the total sample of 54 children indicate regarding prospects of persistence of chorea in such children after 6 weeks' treatment with any of the three drugs?"

Of course, any actual children to whom we applied the results of the Rheumatic Fever Trial might differ in certain undetected respects from the children

in that trial, even if they agreed in all characteristics described in the report of the trial. That is, the sample observed in the trial would not necessarily be equivalent to a random (pure chance) sample of our own population, and the only estimates that we can make pertain to populations randomly represented by the sample observed in the trial. However, chance variation is always present, and is often bigger than investigators imagine. Therefore, although we may underestimate the real "error," the estimates are essential if we are to avoid being grossly deceived by the face value of observed figures.

Experimental Testing of Population Percentages.—Having observed that chorea persisted in 12 out of 54 children (22.2 per cent), we could find by random sampling experiments how likely or unlikely various population percentages might be. Thus, we could use several thousand circular plastic discs, 40 per cent of them marked "CP" (chorea persisted) and 60 per cent of them "CD" (chorea disappeared). After mixing them thoroughly in a barrel, we could draw a sample of 54 discs, and record the numbers of CP's that it contained. After returning the discs to the barrel and reshuffling, we could repeat the process until we had records of 1,000 samples of 54 discs, and we could see how rare, or how common, were samples containing 12 CP's. We do not need to do the experiment, however, because previous experiments of that kind have shown that we can obtain the results mathematically (by using the binomial expansion), and Table I contains the information so obtained. The peak frequency is, of course, at 40 per cent CP's (21 and 22 CP's out of 54). The left and right tails contain, respectively, samples with far fewer, and far more, than 40 per cent CP's.

TABLE I. FREQUENCIES OF RANDOM SAMPLES OF 54 PATIENTS FROM A POPULATION IN WHICH 40 PER CENT OF INDIVIDUALS SHOW CHOREA PERSISTING (CP) AFTER THERAPY

No. of CP's in Sample	10 and less	11	12	13	14	15	16	17	18	19	20	21	22
Frequency of Samples (per cent)	0.1—	0.1	0.3	0.6	1.2	2.1	3.4	5.0	6.9	8.7	10.1	10.9	10.9
No. of CP's in Sample	23	24	25	26	27	28	29	30	31	32	33	34 and more	Total*
Frequency of Samples (per cent)	10.1	8.7	7.0	5.2	3.6	2.3	1.4	0.8	0.4	0.2	0.1	0.1—	100.2—

*The total exceeds 100 per cent owing to rounding errors.

Applying now the customary "5 per cent standard of rarity," we make cut-off points so that the "rare" samples in each tail will not comprise more than 2.5 per cent of the total samples—between CP's 14 and 15 in the left tail and between 29 and 30 in the right tail. The Rheumatic Fever Trial sample (12 CP's out of 54), if it were a random sample from a population containing 40 per cent CP's, would be in the rare class. More than 95 per cent of the random samples would be nearer the population value; i.e., the probability against meeting such rare

samples is more than 95 per cent. On this standard, therefore, we conclude that a population randomly represented by the observed sample would be unlikely to contain as many as 40 per cent CP's.

Confidence Limits of Percentage Frequencies.—In the same way we could answer the question: "Would a population percentage of 30 CP's be unlikely?" By a series of such trials we could then find a boundary percentage, or limit, that would divide populations into (1) those from which the sample might well have come by chance, and (2) those that we would consider unlikely—our confidence in that judgment being represented by the 95 per cent probability specified above. We do not need, however, to go through this step-by-step process, because the required *confidence limits*, derived from, or checked by, binomial expansions, have been tabulated.[6] The relevant information for our sample of size N = 54, with 12 A's (i.e., CP's) is contained on page 30 of that publication,[6] as follows:

N	UPPER LIMIT (95% CONFIDENCE)
52	36.84 per cent A's
55	35.01 per cent A's

For N = 54, the limit must be approximately 35.5 per cent CP's; and the lower limit, from the same table, is approximately 12 per cent CP's. That is to say, the percentage of CP's in a population, randomly represented by our sample, could lie anywhere between 12 and 35.5, but we can assert, with 95 per cent probability, that it would be unlikely to be less than 12 per cent or more than 35.5 per cent. Samples of 50 or 60 do not tell us a very great deal about population frequencies, even when the sampling is strictly random; and samples of 100 are not as reliable as we might think. For example, on page 53 of the tables used above,[6] we find that when a sample of 100 contains 22 per cent of A's, the limits (95 per cent probability) are 14.35 and 31.37 per cent A's.

Confidence Limits of Differences in Frequency.—When an observed difference is not significant, the population percentages may nevertheless differ, and that difference may be in the opposite direction from what the sample seems to indicate. For instance, the Rheumatic Fever Trial report contains the following figures:

TREATMENT GROUP	CASES WITH PERSISTENT CHOREA
Cortisone	2 out of 19 (=10.5 per cent)
Aspirin	9 out of 26 (=34.6 per cent)

Tested in a fourfold contingency table, the difference (24.1 per cent) is not significant at the 5 per cent level (P between 0.2 and 0.1).* That means that al-

*The test, chi-square with Yates' correction for continuity, is shown in many elementary statistics textbooks. For testing samples, equal or unequal, up to size 20, and for testing equal samples up to size 500, more exact results can be obtained, with little or no computation, by the use of tables.[6]

though the observed difference (in favor of cortisone) seems fairly large, we are not convinced that if much larger numbers of the same children had been used, the trial would have shown any real difference; but we should always ask: "If there is a real difference, how large may it be? More technically, what are the confidence limits of the difference?"

To obtain an accurate answer to this question would entail much more elaborate calculation than we need, and a rough approximation to 95 per cent confidence limits can be obtained by using the figures in Table II.

TABLE II. METHOD OF ESTIMATING APPROXIMATE CONFIDENCE LIMITS (95 PER CENT) OF A DIFFERENCE BETWEEN TWO PERCENTAGE FREQUENCIES AFTER A FOURFOLD CONTINGENCY TEST

(D per cent = observed difference)

P FROM CONTINGENCY TEST	TO ESTIMATE CONFIDENCE LIMITS, CALCULATE D ± THE QUANTITY LISTED BELOW
0.9	15.6D
0.8	7.7D
0.7	5.1D
0.6	3.7D
0.5	2.9D
0.4	2.3D
0.3	1.9D
0.2	1.5D
0.1	1.2D
0.05	1.0D
0.04	0.95D
0.02	0.84D
0.01	0.76D
0.001	0.60D

The above figures are based on the fact that, if D is the difference between two percentage frequencies and SD is the standard deviation (standard error) of the difference, then the probabilities of meeting the various values of D/SD, by random sampling from two binomial populations, can be found, approximately, from tables of the Gaussian distribution; e.g., if D/SD = 1.64, the probability P is approximately 0.1.

When P has been found by a chi-square (or more exact) test of a fourfold table, it can be used, along with the observed D, to estimate SD. For example: D = 6.56 per cent; P = 0.1. Therefore, 6.56/SD = 1.64, and hence, SD = D/1.64 = 6.56/1.64 = 4 per cent.

To estimate confidence limits (95 per cent) we write, as with Gaussian distributions, D ± 1.96SD (approximately 2SD). In this example, 6.56 ± 1.96 × 4 = 6.56 ± 7.84 = 14.40 and −1.28 per cent. The above table obviates nearly all this arithmetic, because, in terms of this example, D ± 1.96SD = D ± 1.96 (D/1.64) = D ± 1.2D, as shown at P = 0.1 in the table. Then 6.56 ± 1.2 × 6.56 = 14.4 and −1.3 per cent, as found by the longer arithmetic.

In the cortisone-aspirin comparison, D, to the nearest unit, was 24 per cent, and P was between 0.2 and 0.1. For P = 0.2, Table II gives the confidence limits as D ± 1.5D = 24 ± 1.5 × 24 = 24 ± 36 = 60 per cent and −12 per cent. For P = 0.1, we have 24 ± 1.2 × 24 = 24 ± 29 = 53 per cent and −5 per cent. (The negative values represent aspirin more effective than cortisone.)

These figures indicate that if cortisone is really more effective in children randomly represented by this sample-pair, the difference in percentage of CP's, instead of being 24 as in the sample-pair, may lie between 53 and 60 per cent.

On the other hand, we cannot say with confidence that aspirin is not more effective than cortisone, with a real difference in frequency of CP's of between 5 and 12 per cent.

Even when a difference between samples has been accepted as significant, we should ask the same questions. For example:

TREATMENT	SUCCESSES
A	3 out of 20 (= 15 per cent)
B	12 out of 20 (= 60 per cent)

The difference (45 per cent) is significant (P slightly less than 0.01). For confidence limits, Table II gives $45 \pm 0.76 \times 45$. Substituting $\frac{3}{4}$ for 0.76, we have $45 \pm 34 = 79$ per cent and 11 per cent.

Even samples of 100 do not give us a very precise indication of true (population) differences. For instance, the difference between 59 per cent and 77 per cent, i.e., 18 per cent, is significant (P less than 0.01) when each sample contains 100 individuals, but Table II shows that the true difference may be only one quarter of 18, i.e., about 4.5 per cent.

Confidence Limits of Measurement Data.—Regarding confidence limits of mean differences and other measurement data, the following statements can be made. When data really justify the use of methods derived from the Gaussian distribution (which is not nearly so often as many research workers have been led to believe), we can estimate the 95 per cent confidence limits in the form: $m \pm t$ times the standard deviation (standard error) of m. Here, m stands for the mean difference or other quantity for which we desire confidence limits. For samples containing more than 30 individuals, t is approximately 2. For smaller samples the appropriate value of t is found under $P = 0.05$ in the probability tables familiar to those who apply the t test of significance.

V-9. *Do we intend, after the investigation, to search in the data for factors, effects, or relationships other than those that we contemplated when we designed the investigation? If so, how shall we interpret the findings? What risks do we run?*

Although we avoid minute subdivision of our material at the outset, we do not thereby forfeit all opportunity of comparing effects in finer subsamples, or even in individual subjects, after the data have been collected. For example, this was done after the Rheumatic Fever Trial, by comparing the effects of the three treatments in five subgroups classified by severity of apical systolic murmurs at the start of therapy (absent, and four grades of loudness).

However, unless we plan such searches beforehand, we shall often be led astray. If we hunt around in the data for associations or causal factors that look suggestive, we may find many that are "statistically significant," but all these verdicts may be spurious. Let us suppose, for example, that we looked at the statures of several hundred men, and investigated half a dozen of the tallest and half a dozen of the shortest, with respect to numerous features—anatomic,

physiologic, environmental, and others. Even if all these features had been allotted to our dozen men purely by chance, we ought, of course, to expect 5 per cent of them to show differences that are "significant" at the 5 per cent level, and in many such investigations we would find more than 5 per cent. The results of such searches, instigated by the figures themselves, should be used merely as hints for the planning of an investigation on new material.

VI. NONRANDOM SELECTION METHODS

VI-1. *If the investigation is a survey, how will the samples for comparison (A, B, etc.) be selected?*

Heterogeneous Controls.—In trying to make a survey as like an experiment as possible, we seek for "controls," but the best that we can find are often not very good. Clinically healthy subjects, suitable in age, occupation, and other features, are not easy to obtain; therefore, we often use patients with other diseases. A not uncommon control group is "all other patients," or in an autopsy survey "all other autopsy records." Sometimes the controls are limited to the same time period as the subjects with the disease under investigation, and sometimes age ranges and sexes are made equivalent in the two groups. Such a control is, however, still very heterogeneous—a motley crowd. The contributions from each disease or injury in the control group depend on many unknown factors—the incidence of each condition, numbers exposed to risk, and many factors influencing admission to the hospital; and we have no right to suppose that if we have a great diversity of disorders and large numbers of records, the biases will average out for our benefit.

It is better to use smaller numbers of more comparable groups. For example, it may be possible to take arteriosclerotic heart disease as a control (or comparison sample) when studying certain features in rheumatic heart disease. Sometimes we can use pairs, matched by sex, age, race, environment, and socioeconomic class, but we should always remember that there are probably many other features, perhaps unknown to medical science at present, which, if known, we would use as criteria for matching. Also, there is a risk of selection bias in matched pairs (see Neyman's fallacy, under Question VII-4*).

Vital Statistics as Controls.—Sometimes we are tempted to compare our own figures with national vital statistics (e.g., death rates, disease incidence rates), but the coarse classification of these data (by sex, age, color [white and nonwhite], country, or state) leaves them still too heterogeneous to be trusted far as controls for our particular group of diseased subjects. Moreover, anyone—clinician, laboratory worker, or "nonvital" statistician—who contemplates using official vital statistics for any purpose should first recall the factors that can influence a physician when he creates a "statistic"—such factors as the current fashion in diagnosis and the natural desire to avoid additional distress to a bereaved family by bringing upon it a compulsory autopsy, which would result from certain types of entry.

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*Section VII appears in Part III.

Next, the potential user of official vital statistics should learn something about what happens between the physician's pen and the seemingly authoritative official list. Particularly, he should appreciate the effect of periodic changes in the rules for classifying diseases and causes of death—changes dictated partly by growth of knowledge and partly by increased or decreased interest in certain classes of disease.

To show what can happen when rules are changed, the death certificate information for New York City, January to August, 1949, was classified[7] by (1) the method in use in the immediately preceding years (the fifth revision of the *International List of Causes of Death* and a *U. S. Joint Cause Manual*), and (2) the new sixth (1948) revision of the *International List.* The differences in numbers of deaths attributed to various diseases were expressed in percentage form, (Old − New) × 100/Old. Causes that showed great "decline" were nephritis (70 per cent), diabetes (55 per cent), and syphilis (32 per cent). Great "increases" were shown by rheumatic fever (44 per cent), diarrhea and enteritis (39 per cent), and influenza (31 per cent).

For medical research workers, official vital statistics have their chief value as evidence of apparent trends, suggesting areas where special investigation is desirable.

VI-2. *If the investigation is a survey, what will be the known or conceivable differences between the samples labeled "A," "B," etc., in addition to the factors or features that these letters represent?*

VI-3. *Will the selection of samples for comparison be in any way affected by the contents of the samples, i.e., by the percentage frequencies or measurements that they contain?*

In planning an experiment we may decide to use a specified number of subjects, or we may decide to use as many subjects as become available before a certain date. The sample size is *fixed* or *predetermined.* In clinical trials, in which patients enter in varying numbers and at irregular intervals, we may need to decide, during the experiment itself, the terminal date for the admission of new patients. In the Rheumatic Fever Trial no more children were admitted after Oct. 6, 1952, in the United Kingdom, and after June 15, 1952, in the United States and Canada. The sample size was, nevertheless, predetermined, because it was decided before any conclusions, even tentative, had been drawn from results that had already emerged.

In much laboratory and clinical research there is a habit of experimentation that differs from this. For example, we may apply a certain treatment to a few animals and run a few controls. If we do not feel that the answer is clear cut, we may treat a few more animals, with or without additional controls, until we feel satisfied, from the figures obtained, that there is, or is not, a real difference between the results in the treated animals and those in the controls. Our conclusions may be quite sound, if our background of knowledge is adequate and our judgment is good; but workers in applied biology learned to distrust this kind of experiment thirty years ago, and now many chemists and other experimenters are using less haphazard methods, such as the one employed in the Rheumatic Fever Trial.

After such a haphazard, "open-ended" experiment we cannot, with any logic, hope to establish our conclusions by a test of "statistical significance." Such a test says, in effect: "When a specified number of subjects are separated *strictly at random* into samples of specified sizes, and all subjects are treated alike, differences of such and such magnitude and greater are observed in P per cent of experiments." But our samples in the open-ended experiment are not random. We have selected them because of their contents—the measurements or frequencies that they contain. (Sometimes, in addition, we have rejected certain data because they appeared out of line with the rest, and we believed that they would create a misleading picture.)

At the outset of an investigation hit-and-miss trials are often desirable, or even necessary. They guide us in designing a full-dress experiment with predetermined sample sizes; but the data of the preliminary trials should not be added to the data from the main experiment for analysis.

If data from experiments that fail to qualify for statistical tests are to be published, the only logical way is to present them in considerable detail and state why we draw certain conclusions from them. When editors return manuscripts for statistical tests, and when persons with knowledge of analytical techniques apply tests for which an experiment has not been designed and conducted, they are adding to the spurious statistical arithmetic that abounds in medical journals. Such arithmetic is dangerous because the reader, even a professional statistician, often cannot tell when it is spurious.

VI-4. *How shall we decide when to stop the investigation?*

In the Rheumatic Fever Trial it was decided in advance that each patient was to receive the allotted treatment for six weeks, and that each manifestation (sign, symptom, or result of a laboratory test) was to be recorded at certain specified times during and after therapy. Before the prearranged end point in a therapeutic trial has arrived, the difference in the effects of the treatments may seem so obviously present, or so obviously absent, that we may decide to stop the experiment. Here again, a statistical test is illogical.

Let us suppose that there is actually no difference between the effects of two treatments. Watching the two groups week after week, or month after month, we shall see at certain times a greater frequency, or degree, of improvement in one group than in the other. At other times the two groups will be more alike in response. If we seize on the data for analysis at the times when the groups are most dissimilar, we shall obtain "significant" differences too often. If we analyze the data when the groups are most alike, we shall obtain too many "nonsignificant" differences, whether there is, or is not, a real difference in the effects of the treatments. Our samples are not random, because we have chosen them on account of their contents.

Note: There is coming into medicine an experiment plan, the "sequential" design, whereby we use results already obtained during the experiment in deciding whether to stop or to continue, i.e., to use more subjects. Before the experiment starts we determine, from previous knowledge (of the sequence of random events, of likely frequencies [e.g., of X and not-X], and of the variability

of our material) what amount of evidence, acquired step by step, will suffice to justify the acceptance or rejection of the hypothesis that we are testing, e.g., the hypothesis that there is no difference between the effects of two therapies. Then we conduct the experiment in a very systematic manner, and act according to the rules of acceptance and rejection that we laid down in advance.

This scheme is suitable for experiments in which results emerge quickly (e.g., assessment of short-term benefits of treatment), and it can produce verdicts with less expenditure of time and subjects than is often required by a fixed-sample-size experiment. If, however, the initial knowledge, on which we have based our rules, is unsound, we may be committed to prolonged experimentation, and we cannot, in midstream, convert the experiment to one of fixed-sample size.

REFERENCES

1. Medical Research Council of Great Britain and American Heart Association: Circulation **11**:343, 1955.
2. Mainland, D.: Circulation **16**:784, 1957.
3. Wilson, E. B., Jr.: An Introduction to Scientific Research, New York, 1952, McGraw-Hill Company.
4. Hogben, L.: Chance and Choice by Cardpack and Chessboard, Vol. 1, New York, 1950, Chanticleer Press.
5. Fisher, R. A.: The Design of Experiments, Edinburgh, 1947, Oliver and Boyd, Ltd.
6. Mainland, D., Herrera, L., and Sutcliffe, M. I.: Statistical Tables for Use with Binomial Samples—Contingency Tests, Confidence Limits, and Sample Size Estimates, New York, 1956, Department of Medical Statistics, New York University College of Medicine.
7. Erhardt, C. L., and Weiner, L.: Am. J. Pub. Health **40**:6, 1950.

Notes on the Planning and Evaluation of Research, With Examples From Cardiovascular Investigations. Part III*

Donald Mainland, M.B., Ch.B., D.Sc., New York, N.Y.

VII. RISKS OF BIAS FROM SELECTION RATES

The questions in this section apply to *surveys*. The *selection rate* for A (either a qualitative feature or a measurement) is the percentage of the A-population that comes into the sample of A's that is in the survey. Selection rates and differences between them can cause two types of fallacy, which are associated with the names of Dr. Joseph Berkson[1,2] and Dr. Jerzy Neyman,[3] who demonstrated the mechanisms that produce the fallacies.

Berkson's Fallacy.—It has long been known that the selection rates (admission rates) for different diseases in any hospital, private practice, or autopsy room, differ from each other; that is, our clinical and autopsy samples are biased in the sense that they do not represent the various diseases (or other features) in the same ratio as would be found in the parent population. But we did not recognize the corollary or consequence of that bias until Dr. Joseph Berkson of the Mayo Clinic demonstrated it—that inferences from such samples regarding association between diseases (or between a disease and some other feature) are also biased.

By simple arithmetic it was shown in this JOURNAL[4] how Berkson's fallacy can arise in cardiac autopsy surveys, and the same method has shown how it could mislead us in a search for age differences in blood pressure,[5] in gerontological studies of bone density,[6] and in many kinds of anthropological research.[7] Indeed, it can affect surveys in any field of research or activity whatsoever.

Instead of repeating the demonstration here, we can describe the mechanism without arithmetic—a kind of *competition between selection rates*. Let us suppose that in the population the X's have exactly the same percentage frequency in A's as in B's, that the selection rate for A's is greater than for B's, and that the selection rate for X's is greater than for not-X's. Then, in the survey it will be found that the B-sample contains a higher percentage frequency of X's than does the A-sample, as if the higher selection rate of A's (as compared with B's) has pushed an excessive proportion of X's into the B-sample. This creates a *spurious*

From the Department of Medical Statistics and the Study Group on Rheumatic Diseases, New York University College of Medicine, 550 First Avenue, New York 16, N.Y.

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association, i.e., an association that does not exist in the population. We could, of course, avoid this bias if we knew the various selection rates, but if we knew that much about our population we would not need to make the survey at all.

A Concrete Application of Berkson's Fallacy.—To translate letters into pathologic entities, let us suppose that A and B are two kinds of heart disease, that X represents the presence of a certain blood constituent above or below a certain level (e.g., hypercholesteremia or anemia), and that this abnormality, although equally common in A's and B's, increases a sufferer's tendency to seek medical aid. With the above differences in selection rates, the physician would discover in the B's a higher frequency of the blood abnormality than in the A's.

The picture becomes still more complicated and disturbing when we realize how indirect the selection mechanism may be. For example, X might be some physiologic or morphologic feature or a dietary habit, and it might be commoner in certain groups of persons (socioeconomic, occupational, or racial groups) who tended to seek medical aid, when suffering from A or B, somewhat more readily than did other groups, who were mainly not-X's. Such factors are hard to detect, but they set the stage for Berkson's fallacy.

Other Forms of Berkson's Fallacy.—Three further points regarding competing selection rates should be noted: (1) They cannot only create a spurious association, but can mask an association that actually exists in the population, and even create a spurious association in the opposite direction—X's more frequent in A's in the population, but more frequent in B's in the sample survey. (2) They affect not only frequencies but measurements, as we can see by replacing X and not-X by measurements (X,Y,Z, etc.) such as blood pressures, and by replacing the qualitative features A and B by measurements (A, B, C, etc.) such as ages. (3) Forward-going as well as retrospective surveys can be affected by this bias—if, for example, there is any possibility of interviewers selecting, by some non-automatic process, the subjects to be interviewed, and any possibility of the subjects volunteering, or refusing, to answer questionnaires.

Neyman's Fallacy.—In an experiment or a forward-going survey we compare the percentage frequencies of occurrence of X in the groups A and B between times T_1 and T_2; that is, we study *incidence*. In a retrospective survey we compare the percentage frequencies of X's in the groups A and B at time T_2; that is, we study *prevalence*. We do not know what happened to the A's and B's who started at T_1 but are not met at T_2.

Let us suppose that the incidence of X (some disease or disability) is higher in the A's than in the B's, also that X is more severe in A's than in B's, and therefore AX's are more likely to be removed from the A-group (e.g., by death or change of occupation or locale) than are BX's from the B-group. This is not an unreasonable supposition, because greater susceptibility to a disease often manifests itself not only by greater frequency but by greater severity. Therefore, at time T_2 the prevalence of X may be actually lower in the A's than in the B's. Thus, *difference in prevalence does not necessarily reflect difference in incidence*, and a study of prevalence can mask a real association or create a spurious one.

If, for example, a survey of men aged 50 to 70 years revealed a lower average diastolic blood pressure in heavy (and long-term) smokers than in light smokers

and nonsmokers, several interpretations would be possible, one of them being that smoking had killed many of those whose pressure it had raised, while many of those whose pressure was raised by other factors had survived.

Neyman's fallacy should be remembered when we think of using the "matched pair" technique in seeking for etiology. To illustrate the mechanism, we exaggerate and simplify. Let us suppose that there are equal numbers of smokers and nonsmokers, that equal numbers in each group develop lung cancer, but that smoking is lethal in some other way—for example, by quickly killing those who acquire certain diseases other than cancer. In a survey of lung cancer patients we find equal (or approximately equal) numbers of smokers and nonsmokers, and we match each of them (e.g., by sex, age, occupation and residence) with a person who has one or other of the diseases in which smoking is lethal. In these controls we shall find a higher proportion of nonsmokers than smokers. Such a gross effect would be obvious; but, unfortunately, minor degrees of the same mechanism are hard to detect, and they could produce a "statistically significant" effect.

The following questions are designed to focus our attention on the possibility of risks of selection rate biases.

VII-1. *What could conceivably make the selection rates of A, B, etc., differ from each other?*

VII-2. *What could conceivably make the selection rates of X and not-X (or X, Y, Z, etc.) differ from each other?*

VII-3. *Is there any assurance that competition between selection rates will not lead to Berkson's fallacy?* Note: *If our answer to this question is based on assumptions, we must state them explicitly.*

VII-4. *Visualizing the period before we make the survey, is it conceivable that a phenomenon under study (X, not-X) will eliminate some subjects, by death or other means, and so prevent our including them in the surveys? If so, is it conceivable that this effect will differ in degree in A's and B's? That is, may prevalence mislead us regarding incidence (Neyman's fallacy)?*

VII-5. *If, in spite of the risks of bias from selection rates, and other inevitable uncertainties in surveys (Question V-4, Part II), we intend to conduct a survey, what is our justification for doing so?*

The inherent defects of surveys—their inability to prove a causal relationship, and the ever-present danger of spurious associations—are so discouraging that, in our desire to achieve positive results, we may be tempted to minimize these defects. Particularly, we may shrug off Berkson's and Neyman's fallacies as artificial arithmetic or, at least, as gross exaggerations of danger. Or, on the other hand, we may become so skeptical of all surveys as to feel that very few are worth while. But mankind has learned much from experience (surveys) where experiment has been impossible; and we need neither disregard the dangers nor flee from them.

Before we start a survey we should make very sure of its purposes, immediate and more remote—the *use* that we intend shall be made of an estimate or of an association if we can establish it. The purposes of statistical surveys in medicine

can be enumerated under five headings: (1) To provide, for administrative use, predictive estimates, such as costs of medical care or required numbers of hospital beds. (2) To test the usefulness of a method of diagnosis or prognosis. Even though our sample is biased by selection factors, our conclusions will be applicable to it and to future patients while the selection factors remain the same. (3) To obtain data that will be useful in designing an experiment, e.g., a clinical trial or some animal research that tries to elucidate a causal mechanism that seems to operate in human beings. (4) To obtain suggestions of etiology (including associations between diseases). (5) To assemble and clarify therapeutic experience when a proper clinical trial is not feasible.

It is under headings 4 and 5 that surveys present their greatest risk (and often the greatest vehemence displayed by those who have drawn conclusions from them). Under heading 5, it is astonishingly difficult, especially in chronic diseases, to obtain from case records, questionnaires, or even medical examinations, a useful answer to such an apparently simple question as: "In the patients with disease A that I treated by drug X during the years 1950 to 1953, what were the results?" The numerous problems that we meet in trying to answer such a question are discussed in detail elsewhere.[8]

If we were less anxious to achieve the impossible, we could make more modest, and more logical, claims for the results of surveys.

For example, a cancer epidemiologist might say: "The apparent association between smoking and lung cancer, found in several kinds of survey, coupled with the finding of carcinogens in cigarette smoke, could be plausibly explained as a causal connection. This explanation is sufficiently plausible, in my opinion, to justify (1) recommending that people avoid smoking, and (2) attempting to develop a cigarette that produces less carcinogenic material."

A cardiologist might say: "In my patients with auricular fibrillation a certain ECG pattern (X) occurs so frequently in those who later develop left ventricular hypertrophy, and so rarely in those who do not develop it, that I feel justified in using X as a prognostic sign."

A research worker might say: "The apparent association between high blood lipid level and atherosclerosis, in three meticulously designed and executed surveys, could so credibly be explained as a causal mechanism that I believe animal experiments are justified."

Before starting a survey, however small, we should seek as thoroughly as we can for ways in which selection biases may enter. If, in spite of the risk, we conduct the survey, we should make clear to our readers what specific possibilities of bias we have considered, why we think certain of them are not serious, and, above all, what *assumptions* we are making with reference to such biases.

VIII. SAMPLE SIZES

VIII-1. *What sample sizes will be used in each group (A,B, etc.)?*
VIII-2. *Will the samples be large enough to answer our questions?*
VIII-3. *Will our facilities (personnel, time, money, etc.) suffice to produce the amount of information that we need?*

Information Required Before Estimating Sample Sizes.—Nowadays it is common for investigators to ask: "How many animals [or patients] shall I need in order to obtain a statistically significant result?" Before we can answer that question we have to ask three other questions; which, for verbal ease, we can ex-

press in terms of comparing two treatments, V and W, each on a different group of patients. (1) What level of statistical significance do we intend to use? (2) If treatment W is really superior to treatment V, how great must this superiority be in order to be useful to us? (3) If the real difference is as we have specified in answer to the preceding question, how confident do we wish to be that our experiment will reveal a statistically significant difference?

To answer these questions in any practical way, we must have some knowledge of what our material may be expected to show—for example: the percentage frequency of benefit from one of the treatments under test, or from some other treatment of the same kind of patient; mean values and variabilities, if we intend to assess responses by measurement.

Inasmuch as this article is not trying to cover statistical technique, the problems will be illustrated by enumeration data, but the same general principles are applicable to measurement data.

Obviously, if we seek evidence of a small difference, we shall need larger samples than if we are content to detect evidence of only a large difference. Obviously, also, if we are willing to take a "fifty-fifty" chance of detecting a difference when it really exists, we are willing to risk meeting, in half of our treatment-comparison experiments, nonsignificant ("not proven") differences, or even a few differences that are significant but in the wrong direction, i.e., opposite from the real difference. In other words, we are willing to risk half of our experiments being *unsuccessful*—failing to show a statistically significant difference, in the right direction, when a real difference exists. Most experimenters aim at a much higher percentage of successful experiments, such as 95 per cent.

Tables of Sample Sizes for "All-or-None" Experiments.—For samples containing up to 100 V-treated and 100 W-treated subjects (i.e., with N = 100), and with a significance level of 5 per cent, the required sample sizes can be read from Table X of the book *Tables for Use with Binomial Samples.*[9] For example, if A's are patients benefited by treatment, we find the following figures: If the V-treated population contains 1 per cent A's, while the W-treated population contains 5 per cent A's, with N = 100, the percentage of successful experiments will be 19.4. If the population percentages are 1 per cent A's in V and 15 per cent A's in W, with N = 100, the percentage of successful experiments will be 97.3. If the population percentages are 25 per cent A's in V and 50 per cent A's in W, with N = 100, the percentage of successful experiments will be 94.3.

The Meaning of Sample Size Estimates.—Although the above information was obtained mathematically (by use of the binomial expansion), it does not embody great mystery, for it could be derived by simple, though laborious, experiments. For example, to find the first entry in the above series, we could put into a barrel marked "V" some thousands of plastic discs, 1 per cent of them marked "A" (the remainder being not-A's). Into a barrel marked "W" we could put thousands of other discs, 5 per cent of them marked "A." After thorough shuffling we would take a random sample of 100 from the V-barrel and a random sample of 100 from the W-barrel. We would record the A's and not-A's found in these samples—a fourfold contingency table representing the results of one "therapeutic trial."

We would test the significance of the difference in the proportion of A's in these samples (which, also, could be done by experiment—see notes to Question V-3). Then we would replace the discs in their respective barrels, reshuffle, repeat the process until we had the results of, say, 1,000 such "therapeutic trials," and we would find that about 19 or 20 per cent of them had been "successful," i.e., had produced differences (with more A's in the W-sample than in the V-sample) that were significant (P less than 0.05).

Acquaintance with such figures gives point to a warning, uttered in an editorial[10] on therapeutic trials, but equally pertinent to other experiments and to surveys: "In such trials it is often tempting to add little groups of patients of differing types, here, there, and everywhere, with the object of learning rather more. Although with a statistical design it will certainly sometimes pay to do so, very often the rather more becomes the rather less. Such a trial gives doubtful answers to the many points but no decisive answer to any."

IX. COLLECTING THE DATA

The "data" includes information on everything that we, or others, do to the subjects (or other material) during the investigation. When we question subjects or use records (such as case histories), it includes information on what has previously happened to our subjects (or material), or what is reported to have happened. We must look for: (1) things that can increase variation within the samples that we are going to compare, and that will therefore make our investigation less sensitive to differences between the samples; and (2) things that can create bias.

In this search we are helped by five questions: Who? What? Where? When? How?

IX-1. *Who?—Persons, i.e., observers, subjects, and others involved in the investigation.*

We should ask ourselves such questions as: "Will knowledge of the factors under test introduce bias? If so, how will it be avoided? If more than one observer will be involved, will their differences introduce bias? Will some observers introduce more variation than others?"

In contrast to the standardization and uniformity required in a good experiment, experienced clinicians are aware of the defects common in routine hospital and clinic records—the uncertainty regarding patients' recollection of even major events; the gaps; the unreliability of laboratory and other numerical data; the different standards and different methods of different observers; even the possibility of fictitious figures, such as blood pressures, supplied to fill a blank detected by a records officer after a patient has gone home. We have no right to believe that although individual records are weak, masses of them will be strong—that some kind of averaging process will cancel the defects.

The writer's experience in making routine hospital records, and in trying to use, for investigation, records made by others, has led him to believe that the only records suitable for research are: (1) those kept by a meticulous clinician regarding his own patients, and (2) those kept regarding a particular group of

patients by a suitable and adequately instructed person specially assigned to the task.

Medical training, the distractions and pressures of clinical duties, and the widespread dislike of paper work—these factors make routine case records different from research records. The real purpose of a case record is, however, the benefit of the individual patient, and what might be a serious defect in a research record does not necessarily affect a patient's welfare. In reviewing the *Proceedings of the First International Congress on Medical Records*, Patterson[11] rightly regrets the placing of "too much emphasis on the prospect of research work being made possible by elaborate systems of record keeping which would enable clinicians to get all sorts of statistical material on request." As he says, "The fundamental duty of the records officer is to produce the record when it is wanted, the whole record, and at once."

If we are forced to use routine records in research, we should scrutinize every item that we intend to take from them, and consider its reliability—remembering, for example, that a patient's age, recorded on his first visit, may be carried through unchanged year after year, and that certain x-ray films may be missing because, showing an unusual feature, they were removed for demonstration and never returned.

We cannot hope to reduce bias by omitting the scantiest records. Instead, we may increase it, because the more detailed records may relate to patients with special features in pathology or therapy.

IX-2. *What?—Events.*

It is well to ask ourselves: "Will statements of events contain the whole truth and nothing but the truth?" The notes to the preceding question indicate the answer in many investigations.

IX-3. *Where?—Location and environment.*

If patients or information will come from different sources, this question should recall: (1) the differences (in type of disease, severity, diagnosis, and treatment) between rural areas, small towns, cities, and districts of a city; (2) differences between hospitals (in nomenclature, therapeutic habits, dependability of work); (3) socioeconomic differences (occupation, food, hygiene); (4) racial differences, often associated with differences in location of residence. If animal work is involved, the question should recall differences between laboratories in technique and animal care, as well as environmental differences in the same laboratory.

IX-4. *When?—Time relationships.*

"Every characteristic by which a group of people is commonly classified, except their sex and race, can change with time" (Sartwell and Merrell[12]). Under various other headings, we have already seen how we can fall into traps if we disregard time relationships. Following are a few more examples.

Environmental Differences.—It is not only the individual but the environment that changes with time. A man of 51 today is not only older than a man of 21, but he grew up in a different era of hygiene, diagnosis, and therapeutics, and lived through a war and a depression which the younger man escaped.

Adjustment for Time Relationships.—In a therapeutic trial the effects of

age differences and the duration of disease can be systematically reduced, and then randomization controls the residual bias due to these factors, as well as the possible bias due to the different times at which different patients will enter the trial (seasonal fluctuation in response, changes in hospital personnel, and other time-related phenomena). In a survey, although randomization can help us to avoid certain biases that time may introduce (see below), we are for the most part driven to seek during analysis for time effects, for which we can make some adjustments.

Duration of Follow-Up.—When we compare the frequency of a disease in two groups, we know that we should make allowance for differences in length of time during which subjects have been exposed to the risk of incurring the disease; but an analogous effect in the follow-up of patients is often overlooked. We may read that patients, followed after treatment for periods of 12 months to 5 years, were in such and such conditions when last seen (e.g., percentages improved, not improved, dead). We can see how little this statement tells us if we ask, and answer, two questions: (1) At what time would we make the follow-up observation in an experiment?—At the same time from start of therapy in each subject. (2) Of what population could these percentages be estimates?—Of a highly improbable population composed of patients with the same various durations of follow-up as in the observed cases.

Sometimes we may read, further, that the average duration of follow-up was, say, 24 months. This is an example of how meaningless an average can be. It is no estimate of any real population value. Nor is it of use in comparing the observed percentages with the corresponding percentages obtained by someone else who has followed his patients for the same average length of time. For example, the same average, 24 months, could be found in a series followed for 6 months to 10 years and in another series followed for 20 to 26 months.

Fluctuations in Severity.—In most diseases the sufferer's condition fluctuates in severity, and he is more likely to seek medical aid when his symptoms are more severe than when they are less severe. Therefore, at any particular time after a group of sufferers has come into a physician's hands he should expect to find some of them in better condition than when they first saw him, even if he has done nothing for them. Although very obvious, this phenomenon has been taken as evidence of benefit from treatment, especially in diseases, like rheumatoid arthritis, that are characterized by remissions.

Sequence of Observations.—In clinical trials in which two treatments (or treatment and placebo), A and B, are administered to the same patient in succession, we now know that we must not use the sequence AB (or BA) in all patients. Not only is there risk of carry over of effects from the A-period to the B-period (and sometimes risk of withdrawal effects after A is stopped), but the trend of the disease, up or down, might entirely mislead us in evaluating the AB difference. We have *confounded* (confused or mixed) time and treatment, and confounding can lead to a *post hoc* fallacy.

The simplest way of avoiding the danger is to use sequence AB in half the patients and BA in the other half, allotting the sequences strictly at random. That is, although we use each patient as his own control, we have two groups of

patients, each group acting as a control for the other group with respect to sequence. (This scheme does not, of course, remove risks of carry-over effects, from A to B or from B to A, or in both directions. That problem has to be considered in the light of the particular circumstances of each experiment.)

Instead of the above-described balanced design, an "on-and-off" procedure, repeated several times in the same patient, sometimes seems to give compelling evidence—a relapse every time that the treatment is stopped. If the procedure is strictly double blind, with a placebo administered in the "off" periods, and if the patient's condition changes quickly after change in treatment, our conclusion may be quite sound. But even chronic pain is not a steady state, and our procedure leaves us without exact answers to such questions as: "Have we observed enough patients, or enough change-overs in the same patients?" "How many patients, continued on the treatment, would show fluctuations similar to those manifested by the patients who were taken off it from time to time?"

It is not only in disease that observation sequence can mislead us. For example, the blood pressure of 483 persons, read on two occasions 40 to 80 hours apart, was generally found to be lower on the second visit than on the first—a phenomenon that could be ascribed only to "desensitization" to the sphygmomanometer.[13]

Even in a simple survey, such as the comparison of blood flow by thermocouple on hand and foot, if we cannot make simultaneous records, we should use, in equal numbers of subjects, the hand-foot and foot-hand sequences, with random assignment of sequences to subjects. If three areas or factors are to be contrasted, the six sequences, ABC, ACB, BAC, BCA, CAB, and CBA, can each be used on an equal number of subjects. If there are more sequences than subjects, more complicated designs are necessary, depending on the particular circumstances.

Simple Effects of Time.—Even the simplest time relationships may escape notice. For example, if methods of early detection of a fatal disease are improved, the duration of life from start of treatment will be increased, even if the treatment does not help at all.

IX-5. *How?—Methods.*

Here we have to ask such questions as: "What techniques will be used (laboratory methods, clinical assessment, roentgenography, etc.)? Will there be uniformity of techniques, and of therapeutic and other handling of all samples that are to be compared? Will the methods, including questionnaires and data sheets, be pretested thoroughly?"

Systematic sampling and random allocation are not enough to insure a sound experiment. We must continue, throughout the experiment, to reduce bias and variation systematically. In terms of the Rheumatic Fever Trial,[14] except for the ACTH, cortisone, and aspirin therapies, all groups must be treated uniformly. This does not imply, of course, that we must deprive patients of needed help. For example, five of the aspirin cases were transferred to hormone therapy, and in four other cases a second course of therapy was given. The report contains information on all the fifteen cases in which the treatment and observation schedules were not followed, and it is instructive to see how the investigators handled the data from these cases.

For an unbiased experiment we must use, also, the same methods and times of observation (clinical, laboratory, and radiologic) on all patients. Irregularities of observation times, and gaps in records, not only make the data difficult to analyze but introduce risks of hidden bias. "Every departure from the design of the experiment lowers its efficiency to some extent; too many departures may wholly nullify it. The individual may often think 'it won't matter if I do this (or don't do that) just once'; he forgets that many other individuals may have the same idea" (Hill[15]).

These standards for experiments apply equally to surveys, and if they cannot be sufficiently observed, it becomes questionable whether the survey is worth starting.

IX-6. *When the possibility of bias is suggested by any of the preceding five questions, will the risk be (1) removed, e.g., by standardization of techniques, or (2) controlled by randomization?*

During the conduct of any investigation, whether an experiment or a survey, we should continue this search for the possibility of bias.

If our methods throughout an experiment are uniform, the original randomization may suffice to control all risks of bias, but if there is the slightest risk of uncontrolled bias, we must bring it under control, often by a new randomization. For example, when x-ray assessment, as in tuberculosis, is based on inspection and not measurement, radiologists' standards of assessment can change, even within a short time,[16] and even x-ray measurements by the same observer have been found to display trends. If there is any risk that films from particular treatment groups will be dispatched in clusters to the radiologist, this nonrandom grouping may coincide with a hidden trend in the radiologist's standard of assessment. Such risks can be controlled by placing the films again in the (random) order in which the patients were admitted, or by a fresh randomization.

Although, in a survey, we do not allocate at random the factors under test, randomization is an essential method of bias-control during many surveys. Examples are: random sampling when we do not examine all available patients or records; random order of inspection (or measurement) of x-ray films, electrocardiograms, microscope sections and smears; random assignment to animals of human body fluids that have to be tested and compared by their biologic activity.

X. LOSSES AND REJECTIONS

X-1. *What can we confidently expect to be the percentage completeness of our samples at the beginning and throughout the investigation?*

X-2. *How are we going to insure that the percentage completeness of our samples will be as high as possible?*

X-3. *What numerical effects would the anticipated numbers of lost cases have on our conclusions?*

X-4. *Will records be made of all subjects who, according to our plan, ought to have been in our samples, but who were omitted at the start or were lost later? Will the records give reasons for each omission?*

X-5. *What will be the effects of missing items of data in past records, and of observations omitted during the investigation?*

X-6. *Do we expect to reject any observations? If so, on what grounds? Could these rejections introduce bias?*

In a good experiment we account for all subjects at the end. In a clinical survey the records of certain subjects are often missing or incomplete, and this may introduce serious bias. Ogilvie,[17] discussing the statistics of surgical operations, wrote: ". . . my whole experience [has] left me with profound mistrust of statistics. I have not published mine since I was young and credulous. . . Those who see statistics in the making are well aware how errors may creep in or be pushed in. . . The ailing may be transferred to another ward, another block, another hospital, there to die; they may develop complications and be entrusted to the care of a physician and disappear from the surgeon's series; the unsuccessful cases may be indexed under another diagnosis, or appear in the list of operations done by the assistant. . ."

Without implying purposeful cheating, we should recognize the possibility that circumstances of various kinds may deprive us of records that should, by our specifications, be in our survey. Therefore, before any survey we should ask: "What is the possibility of such losses, and how might they bias our conclusions?"

In follow-up studies, even when many subjects fail to respond to our request for information, we still too often base our estimates on the answers received. This implies the dangerous assumption that the missing cases do not differ from those that we have found. The very fact that some persons have failed to respond should be taken as presumptive evidence that they are (or have been) in some way different from those who responded. Even our inability to discover the deaths of certain subjects probably indicates something different about those subjects.

Regarding failure of response, Bradford Hill[18] wrote: "I would therefore myself infinitely sooner have, say, a one in four sample of the population, of a size thereby which enabled me to pursue relentlessly, and complete the records for, all or nearly all the persons in it, than have to interpret figures derived from survey of the 'whole' population from which finally a quarter was missing." Trying to indicate a maximum permissible lack of response, Doll[19] wrote: "It is perhaps generally reasonable to allow a lapse rate of up to 5 per cent, but a lower rate should always be aimed at and it should be realized that anything appreciably higher may materially bias the results."

When there is lack of response, and little or no information about the nonresponders, the only safe procedure is a double bit of arithmetic. If the possible responses are X and not-X, we first place the missing persons in the X's and then in the not-X's, and compare the two verdicts regarding the factors under test. If we do this with fictitious but realistic numbers before we start our survey, we can convince ourselves of the seriousness of even small losses.

If we replace losses by using other subjects (or readings) we invite bias, but we will be able to see how it may enter only if we carefully scrutinize the circumstances of our investigation. Let us suppose, for example, that for each child who died of cancer below the age of 10 years there is selected at random

another child whose birth date, sex, and place of birth are the same as those of a child who died of cancer. The mothers of all children, cancer cases and controls, are asked whether they had diagnostic pelvic radiography while the children were in utero. Some cases will be lost because the mothers cannot be found or will not submit to interview; but for simplicity let us suppose that this loss will affect equally the cancer cases and the controls, and the mothers who were, and were not, x-rayed. Let us suppose, further, that one woman in six receives antenatal pelvic radiography.

Having traced as many as possible of the children who died of cancer, we must match each of them with a noncancerous child. If we cannot obtain the required information for one of our randomly selected controls, we choose another from our roster. If the missing child was, unknown to us, irradiated in utero, in our second choice we shall have five chances in six of replacing him by a non-irradiated child. Therefore, our control series will become unduly loaded with children who were not irradiated in utero. If our survey contains large numbers of potential controls, the bias will tend to be counteracted because some non-irradiated children, about whom we cannot obtain information, will be replaced by irradiated children; but we should not trust this good fortune without special investigation.

In a much smaller survey, such as an individual clinician might make, the danger may be serious. Let us suppose that the potential control group contains 20 persons, of whom 3 are X's (corresponding to irradiated children in the above example). In our random selection we pick an X, but cannot obtain information about him. Our chance of replacing him by a not-X is now 17 to 2, and a small survey may be badly biased in this way.

CONCLUSION

The foregoing questions help us to see, and partly overcome, the difficulties in research; but they show that many of our tools, especially our survey research tools, even the tools of expert epidemiologists, are still blunt. When discouraged by this picture, we do well to remember the words of the English medical statistician, Professor Greenwood: "The perfect is often the enemy of the good." If we wait until we have perfect tools, we shall never construct anything. If we make the best possible use of the tools that we possess, but always remember their imperfections, we shall not resent criticism of the things that we have constructed by them (our inferences); and we shall continually strive to sharpen our tools and invent better ones. The recent great improvement in therapeutic experimental methods encourages us to hope for advances in survey research also.

REFERENCES

1. Berkson, J.: Biometrics Bull. **2**:47, 1946.
2. Berkson, J.: Proc. Staff Meet. Mayo Clin. **30**:319, 1955.
3. Neyman, J.: Science **122**:401, 1955.
4. Mainland, D.: Am. Heart J. **45**:644, 1953.
5. Mainland, D.: Circulation **16**:784, 1957.
6. Mainland, D.: J. Gerontol. **12**:53, 1957.

7. Mainland, D.: Ann. New York Acad. Sc. **63**:474, 1955.
8. Mainland, D.: Ann. Rheumat. Dis. **14**:337, 1955.
9. Mainland, D., Herrera, L., and Sutcliffe, M. I.: Statistical Tables for Use with Binomial Samples—Contingency Tests, Confidence Limits, and Sample Size Estimates. New York, 1956, Department of Medical Statistics, New York University College of Medicine.
10. Editorial: Brit. M. J. **2**:791, 1948.
11. Patterson, W. G.: Brit. M. J. **2**:140, 1954.
12. Sartwell, P. E., and Merrell, M.: Am. J. Pub. Health **42**:579, 1952.
13. Comstock, G. W., and Kendrick, M. A.: AM. HEART J. **53**:825, 1957.
14. Medical Research Council of Great Britain and American Heart Association: Circulation **11**:343-377, 1955.
15. Hill, A. B.: Brit. M. Bull. **7**:278, 1951.
16. Birkelo, C. C., Chamberlain, W. E., et al.: J.A.M.A. **133**:359, 1947.
17. Ogilvie, H.: Brit. M. J. **2**:663, 1949.
18. Hill, A. B.: *In* The Application of Scientific Methods to Industrial and Service Medicine, London, 1951, H. M. Stationery Office, pp. 7-13.
19. Doll, R.: *In* The Application of Scientific Methods to Industrial and Service Medicine, London, 1951, H. M. Stationery Office, pp. 16-20.

Clinical and Hemodynamic Effects of Cortisone in Patients With Rheumatic Heart Disease and Congestive Heart Failure

David T. Dresdale, M.D., Murray A. Greene, M.D., and Santiago V. Guzman, M.D., New York, N. Y.*

Cortisone and ACTH have generally been used with caution in patients with congestive heart failure of varying etiologies, because of the tendency of these hormones to promote salt retention with secondary water retention and a resulting increase in extracellular fluid volume. Albert, Smith and Eichna[1] have studied the effects of ACTH and cortisone in a series of patients without heart disease. Some of their patients developed fluid retention and, consequently, clinical manifestations and hemodynamic changes resembling, in many aspects, those present in congestive heart failure.

We have had the opportunity to observe the effects of cortisone and ACTH in patients with rheumatic heart disease and congestive heart failure, during a study of the postcardiotomy syndrome in which these agents were used prophylactically and therapeutically.[2] Steroid therapy and/or ACTH had a favorable clinical effect in many of these patients following surgery (cardiotomy with and/or without mitral commissurotomy). It did not precipitate heart failure nor aggravate pre-existing failure. Other patients with clinically inactive rheumatic heart disease who had resistant congestive heart failure, and who were not candidates for cardiac surgery, were occasionally given cortisone, with varying degrees of clinical improvement.[3] Some patients became more comfortable, had less dyspnea and orthopnea, and did not gain weight as readily as prior to receiving cortisone. Less mercurial diuretics were required.

It was these observations that prompted a study of the clinical and hemodynamic effects of cortisone in patients with rheumatic heart disease, pulmonary congestion, and right ventricular failure, and in whom mitral commissurotomy had not been performed. The results of this investigation form the basis of this report.

From the Department of Medicine, Maimonides Hospital of Brooklyn, and the Department of Medicine, State University of New York at New York City, College of Medicine.

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*Postdoctorate Research Fellow of the New York Heart Association. Present address: Department of Medicine, The Bronx Hospital, New York, N. Y.

TABLE I. CLINICAL STATUS BEFORE AND AFTER CORTISONE THERAPY

PATIENT	T*	F.C.	EFFORT DYSPNEA	P.N.D.	ORTHOPNEA	WEIGHT (LB.)	NECK VEIN DISTENTION (gatch)	LIVER SIZE†	EDEMA	MERCURIAL DIURETICS
E.F. Female, age 42 yr. R.H.D., M.S., R.S.R. Cortisone, 54 days	I	III	moderate	occasional	slight	116.5	10°	2	none	occasional
	II	III	moderate	occasional	slight	103.5	10°	2	none	once in 54 days
V.I. Female, age 31 yr. R.H.D., M.S., R.S.R. Cortisone, 25 days	I	III	moderate	none	slight	82.0	90°	2	none	occasional
	II	III	moderate	none	slight	85.0	90°	2	none	every 8 days
B.K. Female, age 39 yr. R.H.D., M.S., R.S.R. Cortisone, 63 days	I	III	moderate	occasional	moderate	116.5	none	2	none	twice per month
	II	II	slight	none	none	121.0	none	2	none	once in 63 days
M.K. Female, age 25 yr. R.H.D., M.I., M.S., A.F. Cortisone, 28 days	I	IV	moderate	occasional	slight	96.5	90°	3	none	once per week
	II	III	mild	less	none	88.0	90°	3	none	every 9 days
G.D. Female, age 36 yr. R.H.D., M.I., M.S., A.F. Cortisone, 49 days	I	II	moderate	none	slight	140.0	none	N	none	none
	II	II	moderate	none	slight	133.0	none	N	none	none
C.D. Male, age 20 yr. R.H.D., M.I., M.S., A.F. Cortisone, 8 mo.	I	II	moderate	none	none	128.0	none	2	none	none (8 mo. before therapy)
	II	II	slight	none	none	143.0	none	2	none	none

*Clinical status evaluated at the time of initial cardiac catheterization (I), and prior to the second hemodynamic study (II).
†Measured as fingerbreadths below the right costal margin.
F. C. = Functional capacity, according to the classification of the New York Heart Association.
P.N.D. = Paroxysmal nocturnal dyspnea. N = Normal.

MATERIALS AND METHODS

Six patients, 5 women and 1 man, with rheumatic heart disease and congestive heart failure are the subjects of this study (Tables I and II). Their ages ranged from 20 to 42 years. Three patients (E.F., V.I., and B.K.) had mitral stenosis with regular sinus rhythm, pulmonary congestion, right ventricular enlargement, and right heart failure. According to the classification of the New York Heart Association for functional capacity, these 3 patients were considered as Class III. The other 3 patients (C.D., M.K., and G.D.) had mitral stenosis and insufficiency with atrial fibrillation, pulmonary congestion, right ventricular enlargement, and right heart failure. Left ventricular enlargement was present in 2 of these patients (M.K. and G.D.). According to the classification of the New York Heart Association for functional capacity, 2 of these patients (C.D. and G.D.) were considered as Class II and 1 patient (M.K.) as Class IV. The possibility of subclinical rheumatic activity was considered in 4 patients (B.K., E.F., G.D., and C.D.) because of either one or more of the following: low-grade fever (100° to 101°F.p.r.), mild leukocytosis, slight-to-moderate elevations in erythrocytic sedimentation rate, and elevated antistreptolysin-O titer (Table II).

TABLE II. LABORATORY DATA BEFORE AND AFTER CORTISONE THERAPY

PATIENT	T*	TEMPERATURE	W.B.C.	E.S.R.	A.S.L.
E. F.	I	N	12,000–14,000	N	N
	II	N	14,500–16,800	40	N
V. I.	I	N	N	N	N
	II	N	N	N	N
B. K.	I	L.G.	14,000	30	N
	II	N	13,000	35	N
M. K.	I	N	N	N	N
	II	N	N	N	N
G. D.	I	L.G.	N	N	625
	II	N	N	N	N
C. D.	I	L.G.	11,000–14,000	19–27	N
	II	N	8,000–15,000	N	N

*Laboratory data evaluated at the time of initial cardiac catheterization (I), and prior to the second hemodynamic study (II).

W.B.C. = White blood cell count. E.S.R. = Erythrocytic sedimentation rate—mm./hour (Wintrobe). A.S.L.= Antistreptolysin-O titer—units/c.c. N = Normal. L.G. = Low grade.

The patients were hospitalized and were semiambulatory. They were observed for 10 to 14 days by one or more of the authors, in order to ascertain the presence of a steady clinical state. During this time routine clinical and laboratory data were obtained. They were placed on a cardiac regimen consisting of a standard low-salt diet and maintenance digitalis. Mercurial diuretics were given whenever fluid accumulation was evident. None of the usual contraindications to cortisone therapy were present.

Physiologic studies of the cardiovascular hemodynamics, utilizing the technique of right heart catheterization, were then performed (Tables III and IV). Duplicate measurements of cardiac output were made in the resting state. Right heart, pulmonary artery, pulmonary "wedge," and brachial artery pressures were obtained using electromanometers* and recorded on a multichannel, direct-writing recorder.* Mean pressures were obtained by electrical integration of the pressure pulses. The point of zero reference for measurement of intracardiac pressures

*Sanborn Company, Waltham, Mass.

TABLE III. CARDIOVASCULAR HEMODYNAMICS BEFORE AND AFTER CORTISONE THERAPY

PATIENT	DURATION OF CORTISONE THERAPY		SURFACE AREA ($M.^2$)	HEART RATE (BEATS/MIN.)	A-V O_2 DIFFERENCE (C.C. %)	O_2 CONSUMPTION (C.C./MIN./$M.^2$)	CARDIAC INDEX (L./MIN./$M.^2$)	CARDIAC OUTPUT (L./MIN.)	BRACHIAL ARTERY O_2 SAT. (%)	TBV	TPV	PPV
E.F.		I R	1.55	100	6.1	155	2.55	3.96	94	5,620	3,170	2,480
		E		105	10.3	242	2.34	3.63	95			
		II R	1.47	95	7.4	159	2.15	3.16	97	4,710	2,570	2,350
	54 days	E*		—	—	—	—	—	—			
V.I.		I R	1.33	95	6.6	139	2.10	2.80	93	3,460	1,900	2,160
		E		120	10.3	240	2.33	3.14	94			
		II R	1.39	90	6.9	126	1.83	2.54	93	3,970	2,270	2,220
	25 days	E		140	12.9	285	2.20	3.07	98			
B.K.		I R	1.51	85	5.3	125	2.36	3.57	95	—	—	—
		E		110	9.5	242	2.55	3.85	97			
		II R	1.53	80	5.0	121	2.41	3.69	95	—	—	—
	63 days	E		110	9.5	268	2.83	4.33	97			
M.K.		I R	1.41	75	6.9	151	2.19	3.09	100	6,200	3,500	2,255
		E		110	11.8	333	2.82	3.98	99			
		II R	1.37	80	7.9	161	2.03	2.78	95	6,520	3,510	2,190
	28 days	E		120	12.7	319	2.51	3.44	96			
G.D.		I R	1.61	75	6.1	148	2.43	3.92	97	5,300	3,080	2,580
		E		85	9.0	260	2.89	4.66	100			
		II R	1.57	70	6.0	146	2.44	3.84	96	4,830	2,760	2,510
	49 days	E		90	9.0	260	2.90	4.55	97			
C.D.		I R	1.68	80	8.1	158	1.95	3.27	98	6,800	3,100	2,690
		E		115	11.3	298	2.64	4.44	94			
		II R	1.75	70	8.6	125	1.45	2.54	96	5,370	2,850	2,800
	8 mo.	E		85	12.9	265	2.06	3.60	100			

*Condition of patient did not permit exercise.

I = Cardiovascular hemodynamics prior to cortisone therapy. II = Cardiovascular hemodynamics following cortisone therapy. R = Resting state. E = During standard exericse.

TBV = Total blood volume (c.c./$M.^2$BSA).

TPV = Total plasma volume (c.c./$M.^2$BSA).

PPV = Predicted plasma volume (c.c./ $M.^2$BSA).

TABLE IV. CARDIOVASCULAR HEMODYNAMICS BEFORE AND AFTER CORTISONE THERAPY

PATIENT	DURATION OF CORTISONE THERAPY		PRESSURE (MM. Hg)							RIGHT VENTRICULAR END-DIASTOLIC	RESISTANCE (DYNES/SEC./CM.$^{-5}$)		
			PERIPHERAL ARTERY			PULMONARY ARTERY			PULMONARY "WEDGE"		TOTAL SYSTEMIC	TOTAL PULMONARY VASCULAR	PULMONARY "ARTERIOLAR"
			S	D	M	S	D	M	M				
E.F.		I R	120	78	90	107	47	68	34	12	1,830	1,370	680
		E	125	80	94	106	50	70	36	15	2,060	1,540	750
		II R	132	82	100	104	37	62	24	10	2,530	1,570	962
	54 days	E*	—	—	—	—	—	—	—	—	—	—	—
V.I.		I R	98	69	85	106	54	74	31	7	2,430	2,110	1,225
		E	104	73	90	116	70	90	37	18	2,290	2,290	1,348
		II R	115	80	93	94	55	68	29	12	2,910	2,140	1,125
	25 days	E	115	85	102	127	83	100	44	25	2,660	2,600	1,450
B.K.		I R	90	55	68	66	34	42	18	3	1,678	940	626
		E	150	75	90	140	62	90	33	3	1,870	1,870	1,185
		II R	112	71	85	80	34	55	24	8	1,795	1,192	672
	63 days	E	—	—	—	152	78	102	45	—	—	1,885	1,054
M.K.		I R	133	78	90	102	52	70	35	15	2,330	1,810	894
		E	158	72	105	128	76	92	50	22	2,050	1,850	845
		II R	128	82	96	95	50	70	—	12	2,760	2,070	—
	28 days	E	148	90	108	128	70	98	—	20	2,588	2,280	—
G.D.		I R	125	77	97	29	14	22	16	6	1,980	450	133
		E	140	88	106	38	21	28	25	8	1,815	480	50
		II R	125	80	96	25	10	16	8	1	2,000	334	167
	49 days	E	140	85	105	26	13	21	13	4	1,834	370	142
C.D.		I R	126	76	93	80	45	58	23	6	2,296	1,418	856
		E	141	89	104	108	61	70	33	6	1,873	1,261	666
		II R	120	72	85	54	33	38	22	6	2,677	1,196	504
	8 mo.	E	125	80	89	87	49	64	33	6	1,977	1,422	688

*Condition of patient did not permit exercise.
I = Cardiovascular hemodynamics prior to cortisone therapy. II = Cardiovascular hemodynamics following cortisone therapy.
R = Resting state. E = During standard exercise.

TABLE V. MEAN VALUES AND STANDARD DEVIATIONS OF VARIOUS MEASUREMENTS OF CARDIOVASCULAR HEMODYNAMICS IN A GROUP OF 29 PATIENTS WITH RHEUMATIC HEART DISEASE

	OXYGEN CONSUMPTION (C.C./MIN./M.^{2})	CARDIAC OUTPUT (L./MIN.)	HEART RATE (BEATS/MIN.)	PRESSURE (MM. Hg)				RESISTANCE (DYNES/SEC./CM.$^{-5}$)	
				PULMONARY ARTERY			PULMONARY "WEDGE" M	TOTAL PULMONARY VASCULAR	PULMONARY "ARTERIOLAR"
				S	D	M			
Mean	−1.6	−0.08	−0.3	−1.8	−0.2	−0.6	−0.8	− 17	−26
Standard deviation	12.1	0.45	5.3	6.1	4.7	4.6	1.9	112	80
95% confidence limit (2 S.D.)	+22.6 to −25.8	+0.82 to −0.98	+10.3 to −10.9	+10.4 to −14.0	+9.2 to −9.6	+8.6 to −9.8	+3.0 to −4.6	+207 to −241	+134 to −186

S = systolic. D = diastolic. M = mean. S. D. = standard deviation.

was taken at 5 cm. below the angle of Louis, with the patient in the supine position. Oxygen consumption was obtained from analysis* of the expired air collected in a Tissot spirometer during 3 minutes of quiet breathing. Blood samples were obtained from the pulmonary and brachial arteries during the time of collection of expired air and were analyzed by the method of Van Slyke and Neill.[5] Cardiac output was derived using the direct Fick principle. Total pulmonary vascular, pulmonary "arteriolar," and total peripheral arterial resistances were calculated according to standard formulae, utilizing the Poiseuille equation where:

$$\text{Resistance} = \frac{\text{Pressure gradient}}{\text{Rate of blood flow}}$$

Resistance is expressed as dynes/sec./cm.$^{-5}$ by the use of conversion factors.† Blood volumes were determined by the direct Evans blue dye (T-1824) method, as modified by Noble and Gregersen.[6]

Response to mild exercise in the supine position was measured after the resting studies were obtained and whenever permitted by the patient's condition. Studies similar to those described above (except studies of blood volume) were repeated from 6 to 9 minutes after the onset of exercise and while the patient was still exercising.

After the control clinical and physiologic studies were obtained, cortisone was administered arbitrarily for 25 days to 9 weeks in 5 patients, and 8 months in 1 patient (C.D.). Cortisone 150 mg. daily was given initially for several days, then a maintenance dosage of 75 mg. daily. One patient (E.F.) was maintained on 50 mg. daily. The previously adjusted and stabilized cardiac regimen was continued during the phase of steroid therapy. This consisted of semiambulation at home or in the hospital, the standard low-salt diet, and digitalis. Mercurial diuretics were given whenever fluid accumulation was evident. Supplementary potassium chloride was given to each patient.

Clinical status (Tables I and II) was re-evaluated and right heart catheterization (Tables III and IV) performed in each patient during the period of cortisone therapy. Methods and techniques utilized were similar to those in the control studies.

Changes in cardiovascular hemodynamics after the phase of cortisone therapy were evaluated in terms of statistical probability. In order to determine whether these changes may have been due to chance variation per se between two studies, or due to the action of an introduced variable (cortisone in the present study), a group of 29 patients with rheumatic heart disease and varying types of valvular disease who had undergone right heart catheterization was used as a control. In each of these patients two "resting" cardiac output determinations were performed at intervals of 21 to 68 minutes (average 42 minutes) in 28 patients and 9 minutes in 1 patient, during a single study and prior to the introduction of any factor which might alter the state of the patient. Chance variations in terms of 95 per cent confidence limits (two standard deviations from the mean variation) were established for various parameters of cardiovascular hemodynamic functions (see Table V). Right ventricular end-diastolic pressure, however, could not be evaluated statistically, because was it only infrequently recorded in duplicate at appreciably long "resting" intervals during a single study.

Alterations in these parameters in the 6 patients who received cortisone were then studied in terms of the respective 95 per cent confidence limits. Right ventricular end-diastolic pressures were evaluated in respect to accepted normal values. It is appreciated that this comparison is not strictly identical because of the difference in time intervals. However, this factor does not appear to represent a major difficulty in view of the fact that the metabolic state of a patient and the hemodynamic values in this study were evaluated on the basis of oxygen consumptions.

Cardiovascular hemodynamics during standard exercise in the initial catheterization and in that following cortisone therapy were compared. Because of changing states, this comparison would not lend itself well to statistical analysis. Instead, the adequacy of the response of the circulation to this type of stress was studied on an individual basis.

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*Scholander gas analyzer.[4]

†1.332 = conversion factor from mm. Hg to dynes/cm.$^{-5}$.

RESULTS

A. *Effects of Cortisone Upon Clinical Status (Tables I and II).*—In 3 patients (B.K., M.K., and C.D.) the degree of exertional dyspnea decreased appreciably during the period of steroid therapy, although no patient became entirely free of this symptom. In 2 patients (B.K., and M.K.) orthopnea disappeared. Bouts of nocturnal dyspnea similarly disappeared in one of these patients (B.K.) and became less frequent in the other (M.K.). In no patient was there an aggravation or precipitation of symptoms of heart failure.

In 3 patients (G.D., M.K., and E.F.) body weight decreased 7, 8.5, and 13 pounds, respectively. In 2 patients (V.I. and B.K.) slight increases in weight occurred (3 and 4.5 pounds, respectively), and in the 1 patient (C.D.) who received cortisone for 8 months a gain in weight of 15 pounds occurred. No patient sustained loss of weight or diuresis when cortisone therapy was withdrawn.

Physical examination of the heart and lungs revealed findings similar to those prior to the phase of cortisone therapy. Electrocardiograms and chest x-rays were similarly unaltered. In 1 patient (B.K.) parenteral mercurial diuretics were required less frequently during the period of steroid therapy. Clinical signs which would suggest increasing fluid accumulation and venous pressure (peripheral edema, neck vein distention, size of liver, moist râles at lung bases) were not aggravated or precipitated (if not present initially) in any patient during the period of cortisone therapy. The gains in body weight in 3 patients (V.I., B.K., and C.D.) appear to be due to increases in tissue mass, since there was no loss of weight or diuresis when cortisone therapy was withdrawn.

In 3 patients (B.K., G.D., and C.D.) fever disappeared during cortisone therapy. Erythrocytic sedimentation rate rose slightly in 1 patient (E.F.) and decreased to normal limits in 2 patients (G.D. and C.D.). In 1 patient (G.D.) the antistreptolysin-O titer, elevated initially, became normal.

B. *Effects of Cortisone Upon Cardiovascular Hemodynamics.*—

1. *Comparison of resting states (Tables III and IV):* One Patient (C.D.) had a decrease in oxygen consumption of 33 c.c. per minute per square meter of body surface area, more than two standard deviations from the mean variation of the control group. Although this single change could be chance variation, the low 24-hour uptake of I^{131} by the thyroid, measured prior to the second cardiac catheterization, would suggest that this decrease in oxygen consumption was significant and could be explained physiologically. No other patient had any significant change in state as measured by this criterion.

In no patient did the cardiac output or heart rate change significantly.

A decline in pulmonary artery systolic, diastolic, and mean pressures beyond the 95 per cent confidence limit occurred in Patient C.D. There was a concomitant decline in pulmonary "arteriolar" resistance.

In 2 patients (E.F. and G.D.) appreciable decreases in pulmonary "wedge" pressures ($>$ 2 S.D.) occurred. One of these patients (E.F.) had a decline in pulmonary artery diastolic pressure of more than 2 S.D. and an increase in pulmonary "arteriolar" resistance. In Patient G.D. the right ventricular end-diastolic pressure had declined 5 mm. Hg. In the latter patient the initially elevated pulmonary artery, pulmonary "wedge," and right ventricular end-diastolic

pressures returned to normal without any change in blood flow or pulmonary vascular resistances.

Patient B.K. had a significant increase in pulmonary artery systolic and mean pressures, with a corresponding increase in pulmonary "wedge" pressure. There was an increase of 5 mm. Hg in right ventricular diastolic pressure.

In Patient M.K. a decrease in right ventricular end-diastolic pressure of 3 mm. Hg, as well as an increase in pulmonary artery resistance, occurred.

An increase in right ventricular end-diastolic pressure of 5 mm. Hg occurred in Patient V.I.

In 4 patients (M.D., G.D., B.K., and C.D.) peripheral arterial oxygen saturations were within normal limits during the resting phase of the initial cardiac catheterization, and no significant changes occurred at the time of the second study. In 2 patients (V.I. and E.F.) peripheral arterial oxygen saturations were minimally decreased during the resting phase of the initial study. In one (V.I.) no change occurred, and in the other (E.F.) a slight rise occurred after steroid therapy.

Plasma volumes were elevated initially in 4 of the 5 patients in whom it was determined. In 3 of these 4 patients (E.F., G.D., and C.D.) there was a decrease in plasma volume of 5, 10, and 12 per cent, respectively, and no change in the other patient (M.K.) after cortisone. The fifth patient (V.I.), who had a slightly diminished plasma volume during the initial study, had an increase of 6 per cent. Total blood volumes changed in a direction quantitatively in proportion to the changes in plasma volumes, except in Patient M.K. In this patient an increase of 320 c.c. in red cell volume occurred after steroid therapy, whereas there was no change in plasma volume.

2. *Comparison of responses to exercise:* Exercise was not performed in Patient E.F. because of symptomatic limitations.

In Patient G.D. a suboptimal increase in cardiac output occurred during both exercise studies. However, although changes in blood flows and oxygen consumptions were practically identical following exercise in both studies, pulmonary artery, pulmonary "wedge," and right ventricular end-diastolic pressures were appreciably less in the second exercise study. The right ventricular end-diastolic pressure did not exceed normal limits during the latter study, whereas it was 8 mm. Hg during the exercise phase of the precortisone cardiac catheterization.

During both exercise studies 3 patients (V.I., M.K., and C.D.) had hemodynamic responses characterized by suboptimal increases in cardiac output, appreciable increases in pulmonary artery, pulmonary "wedge," and right ventricular end-diastolic pressures, and slight increases in pulmonary artery and pulmonary "arteriolar" resistances.

In Patient B.K. a greater increase in cardiac output occurred during exercise in the second cardiac catheterization. Pressures in the lesser circulation and right ventricle were similarly higher, so that no over-all difference in the hemodynamic state existed.

Peripheral arterial oxygen saturation was measured during exercise phases of both studies in 5 patients. No essential changes occurred.

C. *Correlation of Clinical and Physiologic Data.*—Improvement in cardiovascular hemodynamics following the period of cortisone therapy occurred in 4 patients. This improvement was characterized by decreases in pulmonary artery pressures in 2 patients, in pulmonary "wedge" pressures in 2 patients, and in right ventricular end-diastolic pressures in 2 patients. Cardiac outputs did not change in any patient of this series. In 3 of these 4 patients the T-1824 space decreased. Two of these 4 patients noted subjective improvement. The other 2 had no change in symptoms. In 3 patients body weights decreased. The fourth patient (C.D.), in whom the T-1824 space decreased 12 per cent, had an increase in body weight of 15 pounds after 8 months of steroid therapy. In the latter patient, no clinical signs of fluid accumulation appeared during this 8-month period and no diuresis occurred following withdrawal of steroid therapy. The gain in weight can be attributed in great part to increase in tissue mass. This gain in weight has been demonstrated by others to occur in patients who received prolonged steroid therapy. Aikawa and Rhyne[7] observed that prolonged administration of large doses of cortisone to rheumatic subjects may produce clinical signs of hyperadrenalism, usually associated with an increase in body weight. They demonstrated that this gain in weight was greater than could be accounted for by changes in exchangeable sodium content of the body. Further studies of serial measurements of exchangeable potassium content and body weight were made in a group of children with rheumatic fever who received prolonged steroid therapy.[8] Data suggested that total fat content of the body may be increased. Li, Simpson and Evans[9] demonstrated that carcasses of rats treated with corticotrophin show a relative and absolute increase in fat content.

In 2 patients of our series some deterioration in cardiovascular hemodynamics occurred following the period of cortisone therapy. In one of these patients an increase in right ventricular end-diastolic pressure occurred. T-1824 space increased 6 per cent. In the other patient increases in pulmonary artery, pulmonary "wedge," and right ventricular end-diastolic pressure occurred. T-1824 space was not measured in this patient. Cardiac output did not change in these patients. No change in clinical status occurred in one of these patients; in the other, symptomatic improvement was noted. The striking discrepancy between clinical improvement and hemodynamic deterioration in the latter patient is not readily apparent. The steroid-induced euphoria and sense of well-being may be responsible, in part, for the subjective improvement. Both patients had slight gains in weight.

DISCUSSION

The possible therapeutic value of adrenal corticoids in the treatment of congestive heart failure has been reported by others.[10-14] Andrus and co-workers[10] described the effects of corticotrophin in 2 patients with severe mitral stenosis. A marked improvement in respiratory function, appreciable clearing of pulmonary congestion, and a reduction in pulmonary hypertension occurred in both patients. Camara and Schemm[11] and Heidorn and Schemm[12] gave ACTH or cortisone for 10 to 12 days to patients with severe congestive failure of varying etiology. They noted appreciable degrees of sodium and water diuresis during and/or immediately

following treatment in most patients. Use of corticosteroids in 2 patients (of the latter series) with the sodium-dilution syndrome resulted in the induction of a selective water diuresis without an associated sodium diuresis; plasma sodium values returned to normal at the same time. In some patients an increased response to parenteral mercurial diuretics occurred during ACTH therapy. Marked improvement in the clinical status of these patients was concomitantly observed. Reimer[13] administered Prednisone to a patient with arteriosclerotic heart disease with severe pulmonary congestion and extreme anasarca. An immediate increase in urine output occurred, as well as restoration of response to mercurial diuretics. Improvement in signs and symptoms of heart failure occurred concomitantly. Lloyd and Lobotsky[14] reported the use of large doses of lipoadrenal cortical extract in 3 patients with congestive heart failure and edema. A marked diuresis occurred in each patient.

Deterioration of cardiovascular hemodynamics observed in 2 patients of this series would suggest that steroid therapy may be harmful to some patients with congestive heart failure. Albert, Smith and Eichna[1] have demonstrated that the use of corticotrophin and cortisone in noncardiac subjects may result in fluid accumulation, and symptoms and signs resembling those seen in patients with congestive heart failure. Elevations in pulmonary artery, right ventricular end-diastolic, peripheral venous, and peripheral arterial pressures occurred at the same time. That this was not induced heart failure but, rather, congestion of the circulation was suggested by the normal cardiac output and arteriovenous oxygen difference, and by the absence of response to digitalis in 1 patient.

Precise criteria for the selection of patients with congestive heart failure in whom steroid therapy may be beneficial would be of value. These criteria have not as yet been established. A review of the possible mechanisms by which cortisone may have affected the cardiovascular hemodynamics may provide some insight into this problem.

Any direct effect of cortisone upon the myocardium either to diminish existing inflammation (rheumatic myocarditis) or to improve a poorly functioning myocardium may result in hemodynamic improvement. Cortisone and ACTH have been demonstrated to have a favorable effect in many patients with myocarditis.[15-20] Four of the 6 patients in our series had clinical evidence suggesting low-grade rheumatic activity. No systematic relationship, however, existed between the presence of clinical low-grade rheumatic activity and hemodynamic improvement while these patients received cortisone. Although no studies are available concerning the hemodynamic effects of cortisone in patients with overt rheumatic fever, improvement in cardiac output might be reasonably expected if this steroid were to favorably influence any element of myocarditis. All 6 patients in our series had low cardiac outputs prior to cortisone therapy, In no patient did this parameter of hemodynamic function improve during the period in which cortisone was given.

Cortisone may affect the myocardial function directly. Goodman and Gilman[21] state that the steroids may improve the function of striated muscle by mobilizing glucose for energy. Similar effects may exist for cardiac muscle. Dorfman[22] demonstrated that cortisone produced significant effects on glycogen

deposition and muscle work capacity. It has been demonstrated that low concentrations of 9-alpha fluorohydrocortisone have a positive inotropic effect on cat papillary muscle and in the isolated cat heart preparation.[23] Histologically, the cellular integrity of the cat myocardium treated with low concentrations of this steroid was fairly good. In the controls and in those treated with high concentrations, findings of cardiac degeneration were present. The absence of changes in cardiac output following cortisone administration in the patients of this series, however, may again suggest that this steroid does not significantly influence mechanical myocardial activity. This absence of influence was apparent not only in the 3 patients with isolated mitral stenosis and no obvious alteration in left ventricular function, but also in the 3 patients who had mitral regurgitation and probable impairment in left ventricular reserve.

The appearance of hypothyroidism and an enlarged thyroid gland in 1 patient (C.D.) following steroid therapy suggests that cortisone may produce a state of hypometabolism and decreased body demand. An inhibitory effect of cortisone upon the thyroid gland has been demonstrated by others.[24-27] Wolfson and co-workers[24] and Hill and co-workers[25] have demonstrated a decrease in the "accumulation gradient" of I^{131} after moderate doses of cortisone (50 to 100 mg. per day). Fredrickson and associates[26] found a reduction in the 24-hour uptake of I^{131} by the thyroid gland after massive doses of cortisone (500 mg. per day). A decrease in the level of protein-bound iodine has also been observed during cortisone therapy.[24,27]

The reduction in oxygen consumption and reduction in the uptake of I^{131} by the thyroid occurred in Patient C.D. during cortisone therapy. Perhaps this hypometabolic state was influential in favorably altering his symptoms and cardiovascular hemodynamics. No other patient in this series had significant changes in oxygen consumption following steroid therapy. Therefore, the thyroid-inhibiting effect of cortisone cannot be incriminated as the major factor which influenced the clinical or hemodynamic state in this group of patients.

A decrease in total plasma volume occurred in 3 patients of this series. These patients also had improvement in pressures in the pulmonary circulation and right heart. The decrease in plasma volume would suggest that loss of body fluid may have occurred as the primary event, probably by renal mechanisms. Much has accumulated in the literature in recent years to indicate that cortisone, as well as ACTH, may in fact have such an effect on the kidney under certain circumstances.

Davis and Howell[28] demonstrated that both ACTH and cortisone produced an initial loss of salt and water in the intact dog. This loss was accompanied by an increase in glomerular filtration rate. Similar findings were observed in the adrenolectomized dog.[29] Others have reported an initial natriuresis and chloruresis during the administration of ACTH in man[30] and in the rat.[31] Thorn and co-workers[32] found that 17-hydroxycorticosterone enhanced sodium and chloride excretion.

Cortisone appears to have the capacity to stimulate water diuresis. In animals or human beings with adrenal insufficiency, water cannot be excreted at a normal rate.[33,34] In normal animals, when water is given in multiple doses

sufficient to produce water intoxication, diuresis is markedly stimulated by adrenal cortical hormones, and lethal water intoxication is prevented.[35] Gaunt, Birnie and Eversole,[36] in their excellent review of this subject, cite experimental data which indicate that cortical hormones increase diuresis in animals with normal water balance, in those overhydrated, and even in those which have been mildly dehydrated.

The mechanism of cortisone promotion of water excretion may be that of a direct effect on the kidney, or an indirect effect inhibiting the action of the posterior pituitary antidiuretic hormone (ADH). Data cited above has indicated that ACTH and cortisone can produce increases in glomerular filtration rate and renal plasma flow in the dog.[28,29] Deficiencies in renal hemodynamics in adrenal insufficiency can be corrected to varying degrees by adrenal cortical hormones.[37,38] DCA and adrenal cortical extract will decrease tubular reabsorption as measured by creatinine clearance in normal rats.[37] Similar findings were obtained in a human being given DCA.[39] Gaunt and co-workers[36] conclude that although alterations in renal circulation and glomerular filtration may contribute to the increased water excretion following administration of adrenal cortical hormones, inhibition of tubular reabsorption would seem to constitute the major action of these hormones.

Cortisone and related steroids may act indirectly by inhibiting ADH. Cortical hormones tend to antagonize the actions of Pitressin when given simultaneously; and in the absence of cortical hormones, an increased sensitivity to Pitressin has been demonstrated.[40] Lloyd and co-workers[41] produced hyponatremia, edema, water retention, and increased sodium excretion by giving Pitressin to patients with liver disease. Adrenal cortical extract was then given to these patients while they were receiving Pitressin. A marked diuresis and sodium retention occurred. A great deal of additional work concerning the antagonistic action of ADH and adrenal cortical hormones has been reviewed and cited in previous publications.[36,40]

The humoral antagonism cited in the preceding paragraph may play an important role in patients, as well as in experimental animals, having edema or a delayed excretion of water. An increase in urinary antidiuretic substances, believed to consist in large part of ADH, has been demonstrated in experimental cirrhosis in the rat and in cirrhosis in man,[42-44] in eclampsia and pre-eclampsia,[45,46] in nephrotic edema,[47] in premenstrual edema,[47] and in patients having congestive heart failure.[44,48] Some investigators have demonstrated a decrease in urinary corticoids concomitant with the increase in urinary antidiuretic activity.[14,44,49] That this decrease may signify some degree of adrenal insufficiency in some patients with edema and water retention is further suggested by the demonstration of abnormal Kepler-Power water response tests,[44] increased insulin sensitivity,[49] and an abnormal response of eosinophils to hyperinsulinism.[49] Lasche and associates[49] also observed impaired urinary output of corticoids following administration of ACTH to patients with congestive heart failure.

It has been demonstrated that urine from patients with congestive heart failure have increased amounts of the salt-retaining adrenal cortical hormone, aldosterone.[50-52] Luetscher and Johnson[50] have observed that an inverse relation-

ship existed between the sodium output and amount of this sodium-retaining corticoid in the urine. Similar findings have been demonstrated in patients with lipemic nephrosis and cirrhosis with edema.[50,51] An abnormal electrolyte pattern (lowered sodium, higher potassium concentrations) in the saliva[53] and sweat[54] of patients with congestive heart failure further suggests the importance of the salt-retaining hormone in this condition. The effects which cortisone may have in these states ("secondary hyperaldosteronism") have not been adequately investigated. Two separate observations, however, may be important in this regard. Luetscher and Curtis[55] observed that the high output of aldosterone in patients with nephrosis is reduced under treatment with ACTH or cortisone when diuresis ensues. Conn[56] described a patient with "primary aldosteronism" having sodium retention and increased potassium excretion. Compound F and ACTH were administered to this patient. Although a sodium and chloride retention occurred initially, a large urinary outpouring of both ions soon ensued while these agents were still being given.

It thus appears that cortisone and related steroids may act as diuretic agents, capable of producing appreciable losses of salt and/or water under certain circumstances. Previous experimental data, as described, would suggest that these steroids may act either directly on the renal circulation and on the tubular reabsorptive mechanisms or indirectly to inhibit ADH activity and possibly to influence the action of aldosterone. Both ADH activity and aldosterone excretion are increased in congestive heart failure. Other as yet unknown mechanisms may be similarly involved. Cortisone's salt-retaining properties may be outweighed by its diuretic properties under certain abnormal physiologic conditions, e.g., congestive heart failure. Renal hemodynamics and urinary electrolyte patterns were not measured in the patients of the present series. However, the decrease in pressures in the lesser circulation and/or right heart in 4 of the 6 patients while receiving cortisone *without changes in cardiac output*, but associated with a decrease in T-1824 space in 3 of these 4 patients, would suggest that loss of salt and water, probably via the kidney, had occurred as the primary event. An interesting counterpart is suggested by the observations of Albert and co-workers,[1] who noted fluid retention in some normal subjects given ACTH or cortisone. Pressures in the lesser circulation and/or right heart were elevated in these patients, but cardiac output had not changed.

Since certain patients with congestive heart failure may benefit from cortisone therapy, it would seem that further studies in this field are indicated. The criteria for the selection of patients with congestive heart failure in whom cortisone may be beneficial are yet to be established. In this manner the corticoids may be added to the armamentarium for the treatment of heart failure.

SUMMARY

1. The clinical and hemodynamic effects of cortisone were studied in a group of 6 patients having rheumatic heart disease, pulmonary congestion, and right heart failure. Three patients had mitral stenosis; the other 3 had mitral stenosis and insufficiency, and 2 of the latter had left ventricular enlargement.

2. Clinical evaluation and right heart catheterization were performed before and at variable periods of time (25 to 63 days in 5 patients, and 8 months in 1 patient) during steroid therapy.

3. Four patients had slight improvement in cardiovascular hemodynamics characterized by decreases in pulmonary artery, pulmonary "wedge," and/or right ventricular end-diastolic pressures without significant changes in cardiac output while on cortisone therapy. In 3 of these patients plasma volumes decreased. In 2 patients symptomatic improvement in cardiac status occurred. In 3 patients body weights decreased; in 1 patient there was a gain of 15 pounds, which probably represented an increase in tissue mass.

4. Two patients had deterioration in cardiovascular hemodynamics characterized by increases in pulmonary artery, pulmonary "wedge," and/or right ventricular end-diastolic pressures without any significant changes in cardiac output. In one of these patients, plasma volume increased; it was not measured in the other patient. Subjective improvement was noted in one patient. Body weights increased in both patients.

5. Possible mechanisms by which cortisone could have influenced cardiovascular hemodynamics are discussed.

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REFERENCES

1. Albert, R. E., Smith, W. W., and Eichna, L. W.: Circulation **12**:1047, 1955.
2. Dresdale, D. T., Ripstein, C. B., Guzman, S. V., and Greene, M. A.: Am. J. Med. **21**:57, 1956.
3. Dresdale, D. T., Greene, M. A., and Guzman, S. V.: Personal observations.
4. Scholander, P. F.: J. Biol. Chem. **167**:235, 1947.
5. Van Slyke, D. D., and Neill, J. M.: J. Biol. Chem. **61**:524, 1924.
6. Noble, R. P., and Gregersen, M. I.: J. Clin. Invest. **25**:158, 1946.
7. Aikawa, J. K., and Rhyne, M. B.: Circulation **12**:891, 1955.
8. Aikawa, J. K.: Circulation **15**:225, 1957.
9. Li, C. H., Simpson, M. E., and Evans, H. M.: Endocrinology **44**:71, 1949.
10. Andrus, E. C., Newman, E. V., Riley, R. L., Shulman, L. E., and Bahnson, H. T.: Tr. A. Am. Physicians **65**:268, 1952.
11. Camara, A. A., and Schemm, F. R.: Circulation **11**:702, 1955.
12. Heidorn, G. H., and Schemm, F. R.: Am. J. M. Sc. **229**:621, 1955.
13. Reimer, A. D.: Bull. Johns Hopkins Hosp. **98**:445, 1956.
14. Lloyd, D. W., and Lobotsky, J.: J. Clin. Endocrinol. **10**:318, 1950.
15. Garrison, R. F., and Swisher, R. C.: J. Pediat. **42**:591, 1953.
16. Massell, B. H.: New England J. Med. **251**:183-190, 221-228, 263-270, 1954.
17. McEwen, C.: Am. J. Med. **17**:794, 1954.
18. Bunim, J. J.: Bull. New York Acad. Med. **27**:75, 1951.
19. Golden, A., and Hurst, J. W.: Circulation **7**:218, 1953.
20. Kelley, B. C.: A.M.A. Am. J. Dis. Child. **84**:151, 1952.
21. Goodman, L., and Gilman, A.: The Pharmacologic Basis of Therapeutics, ed. 2., New York, 1955, The Macmillan Company, pp. 1659-1660.
22. Dorfman, R.: Physiol. Rev. **34**:138, 1954.
23. Tanz, R. D., Whitehead, R. W., and Weir, G. J., Jr.: Proc. Soc. Exper. Biol. & Med. **94**:258, 1957.
24. Wolfson, W. Q., Beierwaltes, W. H., Robinson, W. D., Duff, I. F., Jones, J. R., Knorpp, C. T., and Eya, M.: J. Lab. & Clin. Med. **36**:1005, 1950.
25. Hill, S. R., Jr., Reiss, R. S., Forsham, P. H., and Thorn, G. W.: J. Clin. Endocrinol. **10**:1375, 1950.
26. Fredrickson, D. S., Forsham, P. H., and Thorn, G. W.: J. Clin. Endocrinol. **12**:541, 1952.

27. Hardy, J. D., Riegel, C., and Erisman, E. P.: Am. J. M. Sc. **220**:290, 1950.
28. Davis, J. O., and Howell, D. S.: Endocrinology **52**:245, 1953.
29. Garrod, O., Davies, S. A., and Cahill, G., Jr.: J. Clin. Invest. **34**:761, 1955.
30. Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G.: J. Clin. Endocrinol. **8**:15, 1948.
31. Bergner, G. E., and Deane, H. W.: Endocrinology **43**:240, 1948.
32. Thorn, G. W., Engel, L. L., and Lewis, R. A.: Science **94**:348, 1941.
33. Gaunt, R.: J. Clin. Endocrinol. **6**:595, 1946.
34. Reforzo-Membrines, J., Power, M. H., and Kepler, E. J.: J. Clin. Endocrinol. **5**:76, 1945.
35. Gaunt, R.: Proc. Soc. Exper. Biol. & Med. **54**:19, 1943.
36. Gaunt, R., Birnie, J. H., and Eversole, W. J.: Physiol. Rev. **29**:281, 1949.
37. Boss, W. R., Birnie, J. H., and Gaunt, R.: J. Clin. Endocrinol. **9**:658, 1949.
38. McGavack, T. H., Saccone, A., Vogel, M., and Harris, R.: J. Clin. Endocrinol. **6**:776, 1946.
39. Zierler, K. L., and Lilienthal, J. L., Jr.: Am. J. Med. **4**:186, 1948.
40. Gaunt, R.: Recent Progress In Hormone Research **6**:247, 1951.
41. Lloyd, C. W., Harris, J. F., and Lobotsky, J.: J. Clin. Invest. **30**:657, 1951.
42. Leslie, S. H., and Ralli, E. P.: Endocrinology **41**:1, 1947.
43. Ralli, E. P., Leslie, S., and Stueck, G. H., Jr.: J. Clin. Endocrinol. **9**:652, 1949.
44. Dochios, M., and Dreifus, L. S.: Am. J. M. Sc. **222**:538, 1951.
45. Teel, H. M., and Reid, D. E.: Endocrinology **24**:297, 1939.
46. Ham, G. C., and Landis, E. M.: J. Clin. Invest. **21**:455, 1942.
47. Robinson, F. H., Jr., and Farr, L. E.: Ann. Int. Med. **14**:42, 1940.
48. Bercu, B. A., Rokaw, S. N., and Massie, E.: Circulation **2**:409, 1950.
49. Lasche, E. M., Parloff, W. H., and Durant, T. M.: Am. J. M. Sc. **222**:459, 1951.
50. Luetscher, J. A., Jr., and Johnson, B. B.: J. Clin. Invest. **33**:1441, 1954.
51. Bartter, F. C.: Metabolism **5**:369, 1956.
52. Laragh, J. H.: Am. J. Med. **21**:423, 1956.
53. White, A. G., Gordon, H., and Leiter, L.: J. Clin. Invest. **29**:1445, 1950.
54. Merrill, A. J.: Am. J. Med. **6**:357, 1949.
55. Luetscher, J. A., Jr., and Curtis, R. H.: Ann. Int. Med. **43**:658, 1955.
56. Conn, J. W.: J. Lab. & Clin. Med. **45**:6, 1955.

Study of the Sequence of Ventricular Activation and the QRS Complex of the Normal Human Heart Using Direct Epicardial Leads

Ennio Barbato, M.D., Fulvio Pileggi, M.D., Antonio Carlos Debes, M.D., Toshyasu Fujioka, M.D., Mário S. Magalhães, M.D., João Tranchesi, M.D., Edgard San Juan, M.D., and Luiz V. Dècourt, M.D., São Paulo, Brazil*

The use of direct epicardial leads allows the solution or the clarification of several controversial problems in electrocardiography. For instance, knowledge of the QRS complex's morphology in different points of the epicardial surface may determine whether tracings of the S_1-S_2-S_3 pattern are due either to a given position of the heart or to an uncommon and peculiar type of ventricular activation. This knowledge will also decide whether the origin of the qR complex recorded in Leads V_1 and V_2, in certain cases of right ventricular hypertrophy, is due to ventricular wall alterations, to a special rotation of the heart, to a special orientation of the precordial electrode near a dilated auricle, to an inversion of the septal activation, or simply to a lack of recognition of an initial embryonic R wave.

Some more important facts can be elicited from the study of epicardial leads; such study may furnish more accurate data on the influence of cardiac rotation on the morphology of thoracic and limb leads. It might contribute also to the solution of whether or not the unipolar leads should be interpreted as a result of several instantaneous mean vectors born in a given point.

So far little attention has been paid to the direct epicardial leads, and their utilization in the past can be criticized as to techniques and cases selected.[2,4,5,7,8,10,14,16,19,20,23,26,28] The greatest mistakes were to locate the electrodes over the pericardium (because it prevents an exact location) and to study patients undergoing pericardial decortication.

In previous papers[3,5] 20 cases were reported: 6, with normal hearts, submitted to pulmonary surgery, and 14 submitted to cardiac surgery. In all of them only a small portion of the pericardium was opened; consequently, the number of points registered was small. However, as we came to know that the technique was safe, we tried larger pericardial openings in subsequent cases.

This paper includes the new series of normal cases.

From the Department of Cardiology, Medical School (Hospital das Clínicas) University of São Paulo, Brazil.

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*From the Department of Thoracic Surgery, Medical School (Hospital das Clínicas) University of São Paulo, Brazil.

MATERIAL AND METHODS

Seventeen patients were selected after clinical, electrocardiographic, and radiologic study showed them to have normal hearts. They were submitted to surgery for pulmonary diseases. Two patients died after surgery and the autopsies confirmed normal hearts.

Unfortunately the epicardium was not explored in its whole surface, as would be desirable, because there were some difficulties due to the surgical opening of the chest. In 7 patients the anterior surface of the right ventricle and the anterior and lateral surfaces of the left ventricle could be explored. In 7 other patients only the anterior surface of the right ventricle was studied, and in 3 patients only the anterior and lateral surfaces of the left ventricle could be explored. Occasionally some points in the auricle were recorded.

TABLE I

	POINT	MORPHOLOGY	Q	R	S	R′	S′	AMPLITUDE	R/S QUOTIENT	I.I.T.
Right Atrium	1	Qr	0.034	0.050				18/6	3.00	0.000
	2	rS		0.008	0.034			0.1/16.8	0.05	0.000
	3	rSR′s′		0.008	0.028	0.064	0.078	2/10/21.5/0.5	43.00	0.000
	4	rSr′S′		0.014	0.036	0.044	0.058	2/5.5/4.7/6	0.78	0.002
	5	rSr′S′		0.012	0.032	0.042	0.052	2/10.5/–1/6	0.17	–0.002
	6	rsR′S′		0.010	0.018	0.041	0.054	4.5/3/22.3/18	1.23	0.000
				R NOTCHING	R	S NOTCHING	S			
Right Ventricle	7	Rs		0.024	0.048		0.062	3/3.2	0.94	0.010
	8	rS			0.028		0.044	3.2/8.6	0.37	0.004
	9	RS			0.022		0.039	7.6/10.6	0.72	–0.006
	10	rS			0.026	0.044	0.050	2.9/6.7	0.43	0.004
	11	rS			0.025	0.044	0.052	3.6/6.5	0.55	–0.004
	12	rS			0.022		0.046	4.3/5.6	0.76	0.004
	13	RS		0.015	0.030		0.043	4.5/5.7	0.79	0.010
	14	rS		0.015	0.036		0.052	2/8.7	0.23	0.010
	15	rS		0.026	0.032		0.050	3.3/9.9	0.33	–0.004
	16	rS			0.021		0.039	3.4/5.5	0.62	0.010
	17	rS			0.020		0.040	2.3/8.8	0.26	0.004
	18	rS			0.034		0.051	5.7/8.6	0.66	0.010

I.I.T. = initial inscription time.

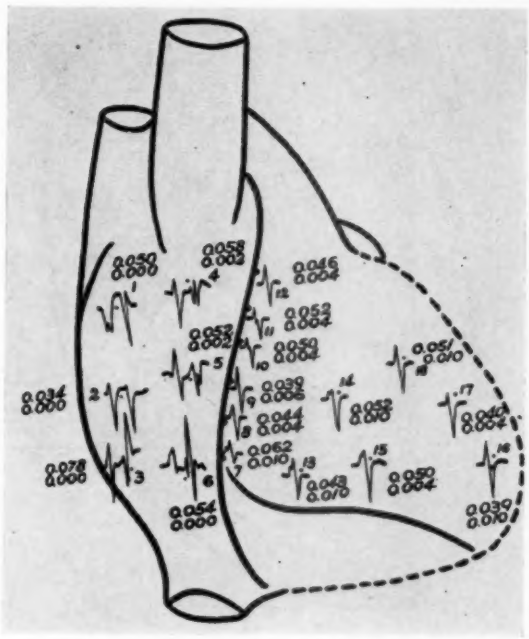
A four-channel Sanborn Poly-Viso Electrocardiograph was used. Recordings were made at a speed of 50 mm. per second. The exploring electrode was a club-shaped platinum wire, mounted in a Ccurnand type catheter.

Simultaneously with the epicardial lead, two standard leads (almost always Leads I and II) and one unipolar limb lead were recorded. Preferentially the chosen leads were the ones with sharp Q waves and free of artefacts.

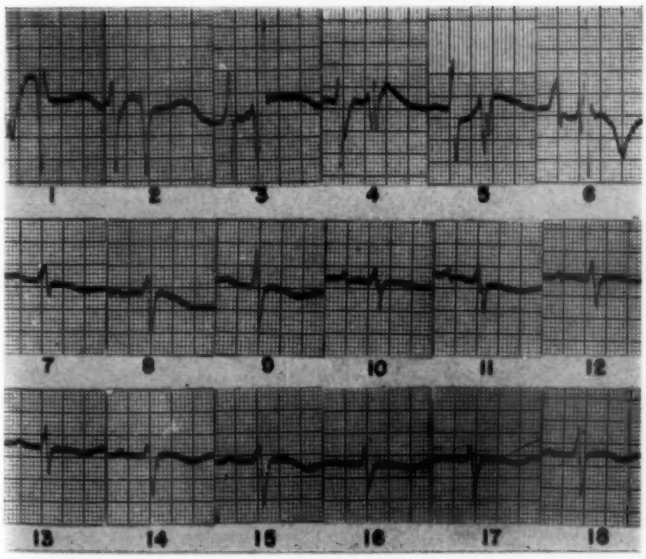
The standardization was generally reduced 4 times, except for certain points where a 20-fold reduction was necessary. With this understandardization, the complexes obtained were smaller than those of the average precordial leads.

Besides the occasional appearance of premature beats during recording of the epicardial leads, no other untoward events were recorded.

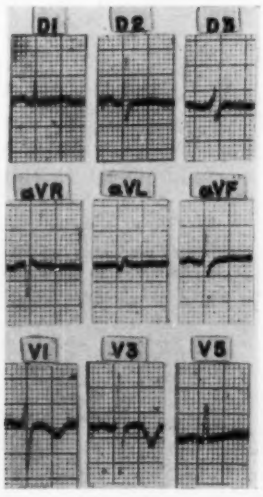
The following data were analyzed in each tracing: (1) the morphology of the QRS complex; (2) the time of inscription of the R wave's zenith, the Q and S wave's nadir, and the peaks of the



A.



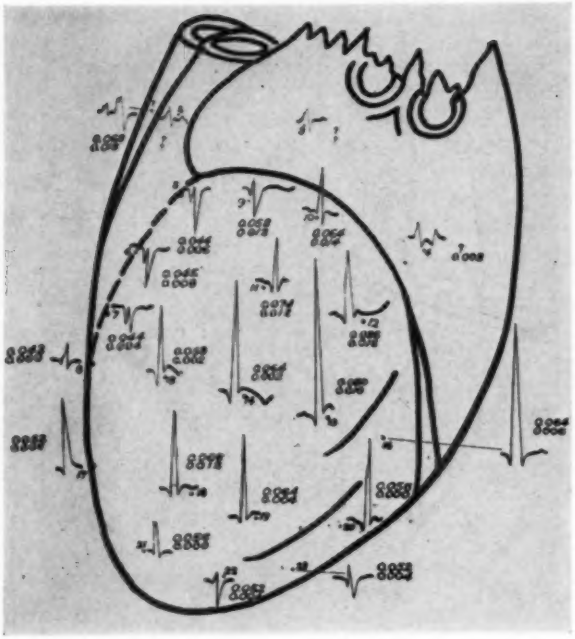
B.



C.

Fig. 1.—*A*, Right anterior ventricular surface. The dotted line represents the sulcus interventricularis. The upper number corresponds to the time of arrival of the stimulus on the epicardial surface. The lower number corresponds to the initial inscription time (see text). *B*, Direct epicardial leads obtained in the same points as the ones in Fig. 1*A*. *C*, Standard leads, unipolar limb leads, and precordial leads of cases corresponding to Fig. 1*A* and *B*.

A.



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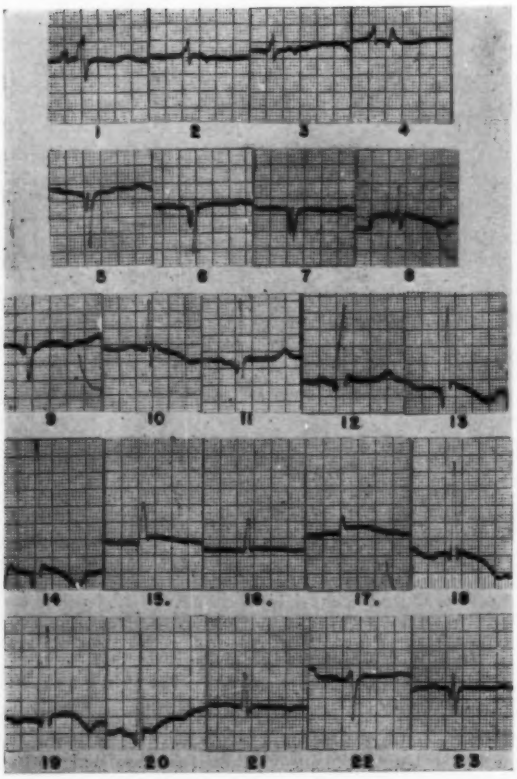


Fig. 2*A* and *B*.—*(For legend see opposite page.)*

notches (all these measurements were related to the onset of the ventricular complex of the simultaneous limb lead, usually Lead II); (3) the height of every deflection; (4) the relation between the amplitude of the R and S waves (R/S quctient); and (5) the measurement of the time lag between the beginning of the QRS complex in an epicardial lead and the onset of the simultaneous limb lead (initial inscription time—I.I.T.).

The anesthesia and epicardial cooling prevented the study of the T wave as expected.

All measurements are plotted in Tables I-III. It should not be forgotten that the standardization was 0.25 cm. to one millivolt, i.e., the complexes obtained are 4 times smaller than they would have been had the usual standardization been used. In those points where a 20-fold reduction was necessary an obviously corresponding reduction was obtained.

Conventional nomenclature is used for morphology; the deflections in parentheses, for instance, Q (r) S, mean that, although they are of significant size, they do not cross the isoelectric line.

In the representative drawings of the cases two numbers are given: the first, corresponding to the time lag in the inscription of the nadir of the S wave, was chosen as an indication of the arrival of the stimuli in the epicardial surface under the electrode. The reasons for such choice have been presented in a previous paper.[31] Recently, Sodi-Pallares and associates (unpublished data) have shown by means of a better technique that the point of arrival of the activation potentials is not at the S wave's nadir, but rather at a point in the downstroke of the S wave, usually located on the third of the way down. This, however, is rarely recorded by an ordinary electrocardiograph. Our measurements are slightly larger, but the direction of the activation is not essentially changed. Therefore, according to the same principle, the R wave's peak rather than the S′ can be used, as has been done classically, without any changes in the results.

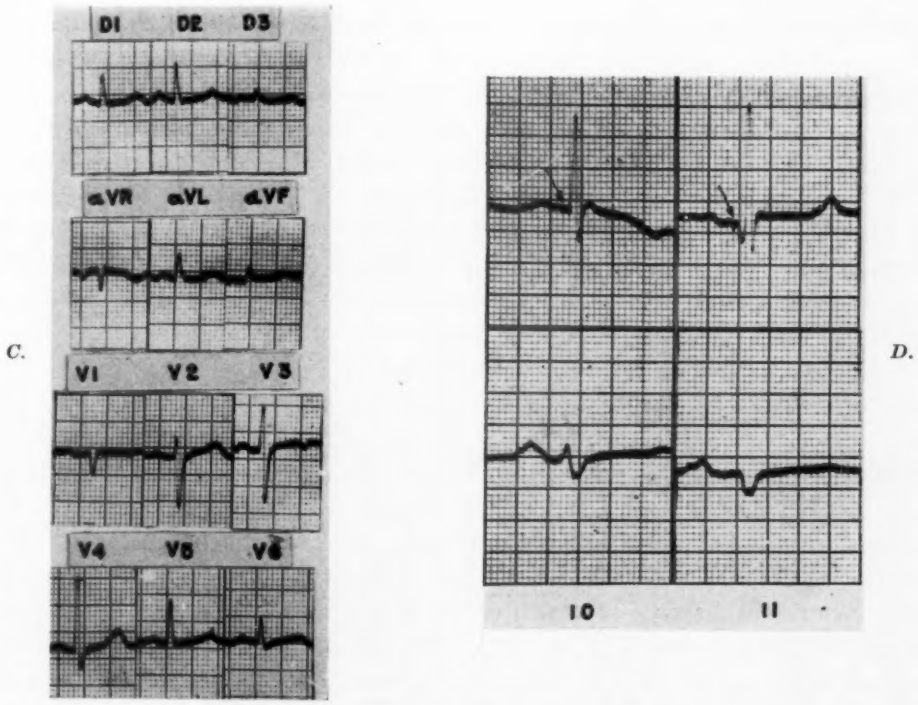


Fig. 2.—*A*, Left anterior and lateral ventricular surfaces. The dotted line represents the sulcus interventricularis. The upper number corresponds to the time of arrival of the stimulus on the epicardial surface. The lower number corresponds to the initial inscription time (see text). *B*, Direct epicardial leads obtained in the same points as the ones in Fig. 2*A*. The numbers with dots mean that the amplitudes are reduced twenty fold instead of fourfold. *C*, Standard leads, unipolar limb leads, and precordial leads of cases corresponding to Fig. 2*A* and *B*. *D*, Points 10 and 11 of Fig. 2*A* amplified. Note slight notching of Q wave.

RESULTS

Since it is impossible to include illustrations of all of our cases, we present only Figs. 1, 2, 3, and 4 and Tables I, II, and III. They are representative of the average results in the common cases and in one case of S_1-S_2-S_3 pattern.

Findings in the Right Ventricle (Fig. 1A, B, and C and Table I).—(1) The first points of activation on the epicardial surface are found more frequently in the trabecular zone and occasionally in the initial portion of the pulmonary conus. (2) The intermediate zone and the remainder of the pulmonary conus are activated simultaneously, shortly after the trabecular zone. (3) The last

TABLE II

	POINT	MORPHOLOGY		R NOTCHING	R	S	AMPLITUDE	R/S QUOTIENT	I.I.T.
Aorta	1	RS		0.028	0.052	0.068	6/6	1.00	0.018
P.A.	2	?		?	?	?	?	?	?
				Q	R	S			
L.A.	3	?		?	?	?	?	?	?
	4	qR		0.026	0.046		2/3.5/0	3.50	0.008
A.S.P.	5	Q(r)S		0.025	(0.034)	0.044	4.5/0/16.0	0.00	0.006
	6	Q(r)S		0.028	(0.040)	0.046	5.9/–1.5/14	0.11	–0.008
	7	QrS		0.024	0.037	0.044	6.7/0.2/9.3	0.02	0.004
	8	qRs		0.012	0.036	0.042	1.7/8.5/3.5	2.43	0.000
			Q NOTCHING	Q	R	S			
Left Ventricle	9	qrS		0.023	0.040	0.058	22/3.5/9.5	0.37	0.012
	10	qRs	0.001	0.032	0.050	0.064	0.3/14.4/4.5	3.20	0.014
	11	qRs	0.001	0.028	0.060	0.074	3/13.8/4.5	3.06	0.012
	12	qRs		0.024	0.072	0.086	1.5/23.4/1.7	13.80	0.016
	13	qRs		0.012	0.046	0.058	4.5/23.5/1	23.50	–0.002
	14	qRs		0.016	0.044	0.064	4.3/38.3/2.0	19.10	–0.002
	15	qRs		0.016	0.056	0.080	1.5/57.5/2.5	23.00	0.010
	16	qRs		?	0.052	0.064	1.5/45/3.5	12.90	–0.006
	17	qRs		?	0.032	0.052	0.8/25/1.0	25.00	–0.006
	18	qRs		0.018	0.046	0.066	1.4/27/2.2	12.30	0.012
	19	qRs		0.014	0.046	0.064	1.2/27.3/3.1	8.81	0.004
	20	qRs		0.016	0.036	0.056	2.3/30/2.5	12.00	0.000
	21	qRs		?	?	0.056	0.3/9/2.6	3.46	0.000
	22	qrS		?	0.036	0.052	0.3/2.2/11.0	0.20	0.004
	23	qRS		0.021	0.036	0.052	2.5/4/7.7	0.52	0.004

I.I.T. = initial inscription time. A.S.P. = anterior septal projection. L.A. = left atrium. P.A. = pulmonary artery.

points to be activated are those in the area between the pulmonary conus and the right border next to the right auriculoventricular sulcus. (4) It seems that the mean process of activation in the anterior surface of the right ventricle is directed upward to the right side.

Findings in the Left Ventricle (*Fig. 2A, B, C, and D and Table II*).—(1) The initial points of activation on the epicardial surface are found at any level in the paraseptal zone; they are activated almost simultaneously with the first portions of the right ventricle. (2) The points near the apex are activated shortly after the paraseptal zone of the left ventricle, at the same or almost the same time as the middle zone of the right ventricle. (3) The lateral half of the anterior surface (intermediate and high portions) and the lateral surface are the last points to be activated. (4) The direction of the mean process of activation is upward from the right to the left in the anterior and lateral surfaces of the left ventricle.

QRS Morphology on the Epicardial Surface.—

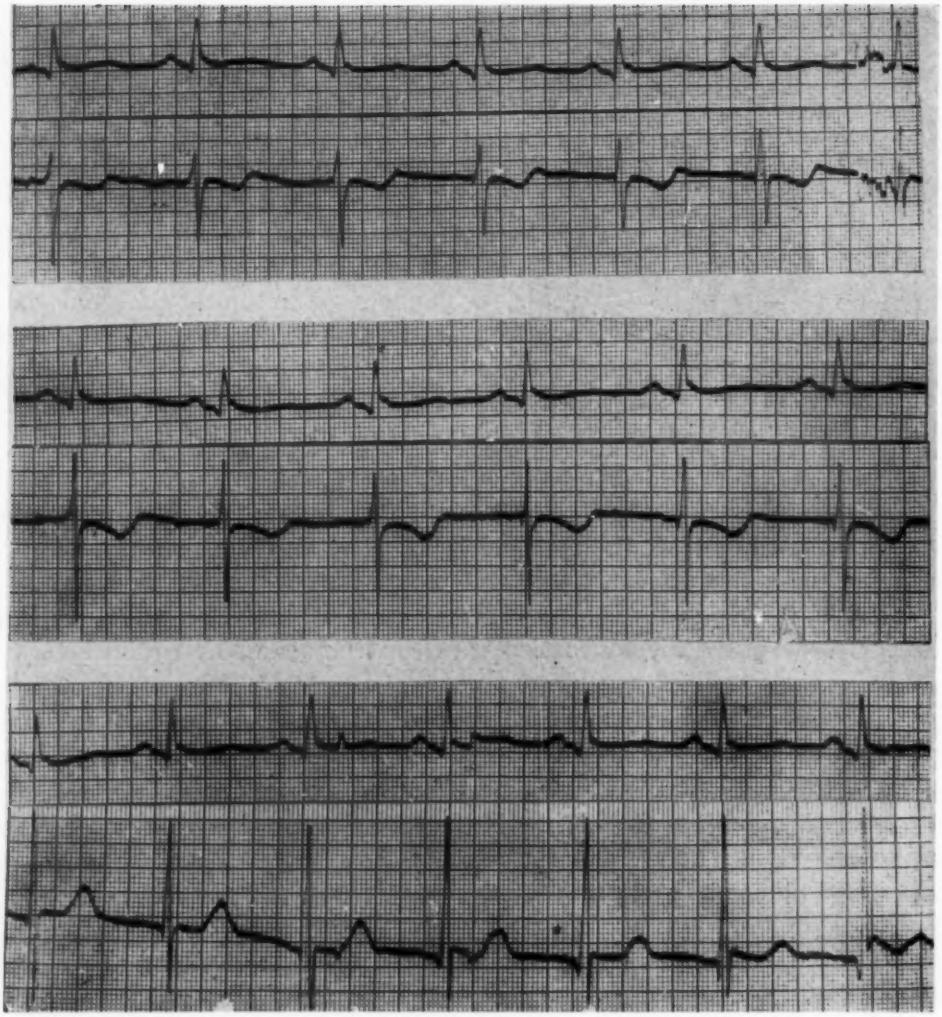
Right ventricle: (1) In the trabecular and intermediate zones, in the apex and the pulmonary conus, the morphology was constantly rS, with notching and slurring in the higher zones that became less apparent toward the apex and trabecular zone. (2) In the area located between the pulmonary conus and the right border, close to the auriculoventricular sulcus, the commonest morphology was rS, usually with a slight notching of r or S. However, RS and Rs complexes were obtained in some cases; both patterns of complexes showed notching or slurring either in the R or in the S wave.

Left ventricle: (1) A qRs or qR was always obtained, with the exception of the paraseptal zones and some areas in the apex. (2) In the paraseptal zones the morphology was qrS and qRS. Occasionally the Q wave was so small as to make its identification impossible in a tracing obtained at a normal speed. (3) The Q wave was more prominent in the higher points; the inscription of its nadir was delayed in the paraseptal area, the delay diminishing as the electrode was moved toward the lateral areas. In the intermediate and lower portions the Q wave became more clearly defined as one moved from the paraseptal to the lateral portions [Fig. 3*A* and *B*]. (4) The S wave became progressively smaller from the paraseptal to the lateral zones [Fig. 3*A* and B]. (5) In one case a notched Q wave was observed in a few points on the left ventricle (Fig. 2*D*).

Anterior projection of the septum: (1) Only one case was studied in its higher portion over the anterior descending branch of the left coronary artery. Q (r) S and QrS complexes were obtained. (2) Another case showed, over the descending branch, complexes of the rS, RS, and qRS patterns. (3) In a third case (Fig. 3*A* and *B*), when the upper part of the septum was studied, the morphologies obtained as the electrode was moved from right to left were rS (with slurring of the ascending limb of R), qrS, and qRS. Lower levels yielded RS complexes with slurring of the ascending limb of R and qRS morphology when the electrode was moved to the left.

Right atrium: The right atrial morphologies were extremely variable in different cases and in the different areas explored; QR, rsr′, Qr, rSR′S′, and rS were indistinctly obtained, and more rarely qR.

A.



B.

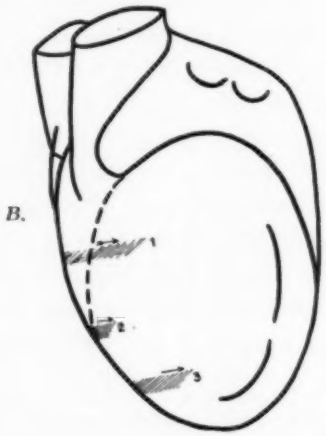
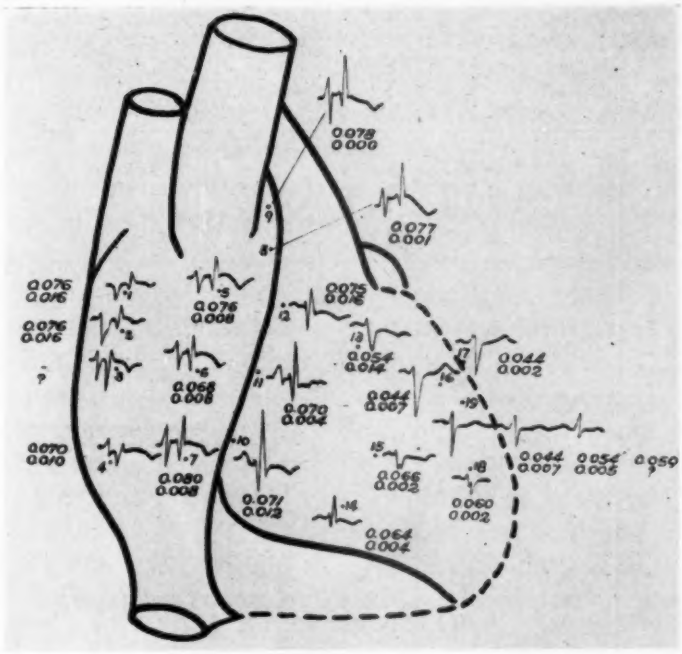
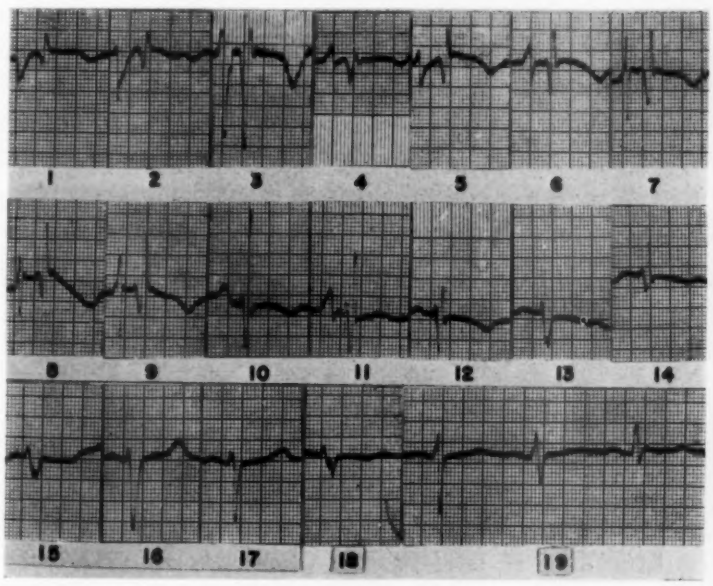


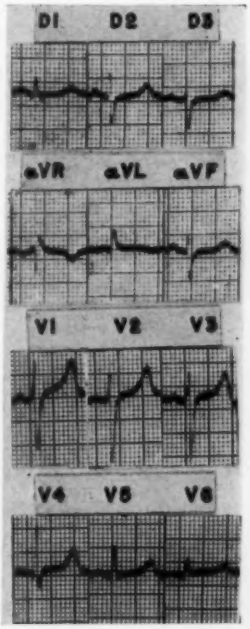
Fig. 3.—*A*, Tracings obtained by moving the electrode in three levels, as indicated in Fig. 3*B*. *B*, The electrode in *A* was moved along the lines represented in this figure.



A.



B.



C.

Fig. 4.—*A*, Right anterior ventricular surface in a case of prominent S_2-S_3. Autopsy revealed a normal heart. *B*, Direct epicardial leads obtained in the same points as the ones in Fig. 4*A*. *C*, Standard leads, unipolar limb leads, and precordial leads of cases corresponding to Fig. 4*A* and *B*.

TABLE III

	POINT	MORPHOLOGY		Q	R	S	AMPLITUDE	R/S QUOTIENT	I.I.T.
Right Atrium	1	QR		0.037	0.059		2.5/4/0	4.00	0.016
	2	QR		0.035	0.059		4.3/4/0	4.00	0.016
	3	Qrs		0.038	?		5.5/1.3/0.2	6.50	?
	4	Qrs		0.031	0.055		5.8/1.3/0	1.30	0.010
			R	S	R′	S′			
	5	rSR′s	?	0.036	0.059	0.076	0.5/5.3/7.4/1.1	6.70	0.008
	6	rSR′s′	0.020	0.032	0.056	0.068	1/8.3/8/1	8.00	0.008
	7	rSR′s′	?	0.034	0.063	0.080	1/8.4/9/1	9.00	0.008
Right Atrial Appendage	8	rsR′s′	?	0.036	0.061	0.077	1/5.3/12/0.5	24.00	0.001
	9	rsR′s′	0.018	0.032	0.061	0.078	1/5/13/0.3	43.30	0.000
Right Ventricle	10	rSR′s′	0.020	0.038	0.060	0.071	2/10/23/2	11.50	0.012
	11	rSR′s′	0.017	0.037	0.055	0.070	2/9.5/15.5/1.5	10.30	0.004
	12	rSR′s′	0.022	0.042	0.006	0.075	1.6/9.5/6/1.5	4.00	0.016
			R		S				
				1°	2°	3°			
	13	rS	0.019	0.037	0.057	0.054	2.4/6.5/5.5/7	−0.79	0.014
			R	S	R′	S′			
	14	rSR′s′	0.016	0.032	0.054	0.064	1.4/3.5/7/1	7.00	0.004
			R		S				
				1°	2°	3°			
	15	rS	0.014	0.046	0.057	0.066	1.7/5/−2.7/5	−0.54	0.002
			R			S			
	16	rS	0.013			0.044	2.5/17.3	0.15	0.007
				R		S			
			1°	2°	3°				
	17	rS	0.014	0.026	0.036	0.044	2.3/14.3	0.16	0.002
			R		S				
				1°	2°	3°			
	18	rS	0.014	0.042	0.048	0.060	1.8/2.5/−0.1/5	−0.02	0.002
A.S.P.			R SLUR	R		S			
	19	rS	6.026	0.034		0.044	5/13.3	0.37	0.007

Pulmonary artery: Tracings from the pulmonary artery were studied in a few cases; rSr′ morphology or polyphasic complexes not well identified were obtained.

Right and left atrial appendages: Few studies were carried out in these areas. The morphologies found were QR, rsr′, qrS, and qrSr′S′.

Aorta: One case was studied at a single point over the aorta. The complexes were of the Rs type, with marked notching of the R wave.

Amplitude of the QRS Complexes.—(1) With the exception of the lateral intermediate and the higher points of the left ventricle, a reduction to one fourth of the normal standardization is sufficient to obtain complexes of approximately the same magnitude as those obtained with precordial leads. (2) In the intermediate and upper areas of the anterior and lateral surfaces of the left ventricle a standardization equivalent to one twentieth of the original had to be used when working in adults (with the exception of a 9-year-old patient). The QRS complexes thus obtained had a slightly lower amplitude as compared to complexes obtained in precordial leads. (3) The trabecular zone exhibited complexes of a relatively higher amplitude than did the rest of the points studied in the right ventricle. (4) Occasionally there was an extreme disproportion, sometimes more than 80 times, between the R wave obtained in the intermediate and high lateral portions of the left ventricle and that observed in the right ventricle.

The Time Lag Between the Onset of Inscription of QRS Complex in the Epicardial Leads and the Onset of the Inscription of the QRS in the Reference Lead (I.I.T.).—It should be noted that the inscription of the complexes in the epicardial leads might be earlier, later, or concomitant with their inscription in the lead used as reference (Lead II).

Tracings of the S_1-S_2-S_3 Pattern.—In one case (Fig. 4*A* and *B* and Table III) there was a deep S wave in Leads II and III resembling the so-called S_1-S_2-S_3 pattern. At autopsy the heart was normal. The morphology in the trabecular and intermediate zones was rS. In the basal portions and in the right border of the right ventricle rsR′S′ complexes were obtained. In this particular case the difference between the time of activation of the trabecular zone and that of the base of the heart was larger than in the other cases.

DISCUSSION

The currently accepted concepts of the activation process of the human heart are based almost exclusively on animal experimentation.[7,9,15,18,19,23,25,29,30,34,38] However, the normal ventricular activation in man is quite different from that in the dog, probably because of the difference in the thickness of the myocardium or the difference in distribution and penetration of Purkinje's network.

Still greater are the differences in morphology between man and dog, and it is impossible to correlate them. In man, one obtains predominantly a rS pattern in the whole anterior surface of the right ventricle, while in the dog it is possible to obtain RS and Rs patterns in certain zones.[30] QRS patterns without Q are not obtained in the anterior and lateral surfaces of the left ventricle in man,

while in the dog they can be obtained in the apex of the heart. It is possible that in the human diaphragmatic surface[4] one can obtain such patterns (QRS without Q).

In some cases complexes are found with later R waves in the base of the right ventricle. They were obtained as a usual finding by Alzamora Castro and associates,[1] who worked with the unopened pericardium. These investigators admitted that the identification of the points under study was not accurate and that the pericardial leads are quite susceptible to local short circuits. Besides the factors already mentioned by these workers, we think that the greater or lesser occurrence of such complexes may be due to racial and constitutional factors. In our patients, delayed R waves in the multiple thoracic leads are found less frequently than in other series.

Polyphasic QRS complexes are also found in the base of the right ventricle in cases of S_1-S_2-S_3 pattern. As Grant[12,13] pointed out, these findings suggest, at least in some cases, that the S_1-S_2-S_3 pattern represents a different and peculiar type of normal activation and does not indicate a particular position of the heart.

We obtained QRS complexes of the W type only in the anterior superior portion of the septum or in its neighborhood, and qrS complexes only in the left paraseptal zone. This is contrary to Groedel and Borchardt's findings of W and qrS types in different points of the epicardial surface.[14] Such morphologies led us to analyze Myers' findings[21,22] of similar patterns in precordial leads, simulating myocardial infarction, in cases of right and left ventricular hypertrophy. He correctly assigns the W morphology to the upper part of the septum. In certain conditions great rotations of the heart are likely and the electrical variations registered in precordial leads may be identical to those registered in the upper part of the septum (W) or in certain left paraseptal portions (qrS).

Myers attributes this W morphology to an equilibrium of forces between both ventricles at the onset of ventricular activation. This would cause the disappearance of either the Q wave or the R wave which should be just beginning to inscribe at this point. However, it is very likely that this morphology is simply the result of an early myocardial activation in this portion, due probably to this area's greater richness in Purkinje fibers.

Looking at the QRS morphologies as a whole in all points of the anterior and lateral surfaces of the heart, two well-defined zones can be described—one of prevailing negativity and another of prevailing positivity. This is similar to what happens in the thoracic leads, as pointed out by Grant.[11] The two zones are separated by a transitional one which is located, in normal cases, in the left portion of the anterior projection of the septum and left paraseptal areas.

Occasionally, high and delayed R waves are obtained in the base of the right ventricle; this is an unexpected finding because in such areas one should obtain predominantly negative complexes. In such cases the QRS complex on any point of the epicardium cannot be interpreted as a result of several instantaneous mean vectors born at a given point, as has been done in relation to the thoracic leads. It is also difficult, in many cases, to explain by means of single instantaneous vectors the great disproportion between the amplitude of the prevailing positive complexes and prevailing negative complexes.

Some restrictions should be made on the point of view of representing the activation spread as three main vectors,[24] especially in regard to the so-called first or septal vector. The apex of the Q wave is used to determine spatial orientation of the first vector; however, this is not correct because its registration is not synchronous in all leads. This invalidates the hypothesis, based on such vector determination, that the septal activation might spread from right to left in some cases. The time lag for the Q-wave inscription includes, undoubtedly, not only the septal activation but also the activation of the juxtaseptal parts of both ventricles.

The last cardiac vectors are related to the posterobasal portions of the left ventricle, to the septum, and to the right ventricular areas of late activation. The right ventricular contribution to the formation of these vectors has been related to the crista supraventricularis by Kossmann and associates.[17] We have not found in the right ventricular surface any points which are activated at the same time or later than the last portions of the left ventricle. Since it is impossible to explore the crista supraventricularis, we are not in a position to comment on this subject. However, if Kossmann's assertions are true, the fundamental factor is not the thickness of the crista because, in our cases, it neither equals nor exceeds the thickness of the lateral and posterobasal portions of the left ventricle. The penetration of Purkinje's network into this region could be the factor involved.

We should like to emphasize once more the importance and accuracy of the studies based on epicardial leads. Such reasoning is corroborated by one of Helmholtz's laws[32]: in a volume conductor the integral of the surface equals the integral of the volume, that is, the surface phenomena closely reflects the events occurring in the myocardium.

SUMMARY AND CONCLUSIONS

In 17 patients with normal hearts submitted to pulmonary surgery the epicardial leads were recorded with the idea of studying the spread of ventricular activation and QRS morphologies in different points of the anterior and lateral ventricular surfaces.

The activation spread of the whole heart in the majority of cases was as follows: the septum, the right paraseptal zone, and some portions of the left paraseptal zones were the first to be activated, followed by the other parts of the left paraseptal zone, apex, right ventricular intermediate zone, and pulmonary conus, and finally by the left ventricular intermediate zone and upper levels of the left ventricular lateral portions. In some cases the activation of the areas near the right border of the right ventricle and the auriculoventricular sulcus was delayed, and in other cases the pulmonary conus was activated early. The diaphragmatic surface was not studied.

In the anterior surface of the right ventricle the predominant QRS-complex morphologies found were rS patterns. In some cases RS with slight notch or polyphasic patterns with delayed RS in the base of the right ventricle were also found.

In the anterolateral surface of the left ventricle the morphology was either qRs or qR, and qRS and qrS in the paraseptal portions. Complexes without Q waves were not found in these surfaces. In the upper portion of the anterior projection of the septum we recorded either notched QS or QrS and QRS.

The electrocardiographic transitional zone was found in the lower halves of the left portion of the anterior projection of the septum and of the left paraseptal zone (with initial Q).

The amplitude of the epicardial leads was 4 to 20 times larger than the normal, and the largest amplitudes were found in the lateral surface of the left ventricle.

In one case of S_1-S_2-S_3 pattern the activation spread was quite different from the normal one. In the basal portion and in the right border of the right ventricle rsR′S′ complexes were obtained.

REFERENCES

1. Alzamora Castro, V., Abugattas, R., Battilana, G., Rubio, C., Bouroncle, J., Zapata, C., Santa-Maria, E., Subiria, R., Binder, T., and Paredes, D.: Am. Heart J. **46**:790, 1953.
2. Boden, E., and Neukirch, T.: Arch. f. ges. Physiol. **171**:146, 1918. Cited by Meek and Wilson: Arch. Int. Med. **36**:614, 1925.
3. Barbato, E.: Estudo da ativação ventricular normal e patológica, Thesis, São Paulo, 1952.
4. Barbato, E.: Rev. Med. Cir. S. Paulo **17**:17, 1957.
5. Barbato, E., Dècourt, L. V., and Pileggi, F.: Am. Heart J. **46**:928, 1953.
6. Barker, P. S., Macleod, A. G., and Alexander, J.: Am. Heart J. **5**:720, 1930.
7. Burchell, H. B., Essex, H. E., and Pruitt, R. D.: Circulation **6**:161, 1952.
8. Carouso, G. J., Chevalier, H., Latacha, B. I., and Lenègre, J.: Circulation **5**:48, 1952.
9. Eyster, J. A. E., and Meek, W. J.: Am. J. Physiol. **134**:513, 1941.
10. Feil: Quoted from Hein and Reavis.[16]
11. Grant, R. P.: Circulation **2**:676, 1950.
12. Grant, R. P., and Estes, E. H.: Spatial Vector Electrocardiography, Philadelphia, 1951, The Blakiston Company.
13. Grant, R. P.: Circulation **7**:890, 1953.
14. Groedel, F. M., and Borchardt, P. R.: Direct Electrocardiography of the Human Heart and Intrathoracic Electrocardiography, New York, 1948, Brooklyn Medical Press, Inc.
15. Harris, A. S.: Am. J. Physiol. **134**:319, 1941.
16. Hein, G. E., and Reavis, J. C.: Circulation **1**:964, 1950.
17. Kossmann, C. E., Berger, A. R., Rader, B., Brumlik, J., Briller, S. A., and Connelly, J. H.: Circulation **2**:10, 1950.
18. Lewis, T., Meakins, J., and White, P. D.: Phil. Trans. Roy. Soc. **206**:181, 1915.
19. MacGregor, M.: Brit. Heart J. **12**:351, 1950.
20. Magri, G., Brusca, A., and Angelino, F. P.: Presse med. **66**:1349, 1955.
21. Myers, G. B.: Circulation **1**:844, 1950.
22. Myers, G. B.: Circulation **1**:860, 1950.
23. Nylin, O., and Crafoord, C.: Cardiologia **6**:136, 1942.
24. Peñaloza, D., and Tranchesi, J.: Am. Heart J. **49**:51, 1955.
25. Rodriguez, M. I., and Sodi-Pallares, D.: Arch. Inst. cardiol. México **6**:756, 1953.
26. Sampaio, A., Bertolanni, V., and Kneese de Melo, H.: Am. Heart J. **46**:790, 1953.
27. Schaefer, H.: Das Elektrokardiogramm. Theorie und Klinik, Berlin, 1951, Springer Verlag.
28. Scharer, R. F., González Segura, R., Guardo, A. H., Marin, M., Ressia, T. P., and Romano, F. J.: Considerations on Epicardial Electrocardiograms in Man Both in Normal and Pathological Cases. Review, Fourth Interamerican Congress of Cardiology, Buenos Aires, 1952.
29. Scher, A. M., Young, A. C., Malmgren, A. L., and Erickson, R. V.: Circulation Res. **3**:56, 1955.
30. Sodi-Pallares, D., Barbato E., Estandía, A., and Espino, J.: Arch. Inst. cardiol. México **19**:688, 1949.
31. Sodi-Pallares, D., Barbato, E., and Delmar, A.: Am. Heart J. **39**:387, 1950.
32. Sodi-Pallares, D.: Am. Heart J. **51**:647, 1956.

Clinical Value of Ballistocardiography

A. Fidler, M.D., A. N. Bhargava, M.B., B.S., and P. Parent, M.D., Ottawa, Canada

Ballistocardiography may be defined as a study of the functional quality of the heart beat through the recording of the motions imparted to the body by the ejection and flow of blood through the circulatory system.

The movement of the body with every heart beat has been known to exist much before the first recording of Gordon[9] in 1877. C. H. Parry had observed this in a patient with hyperthyroidism in 1786. Starr,[28] in 1939, described such records under the term of "ballistocardiogram."

During the years between 1877 and 1939, various workers had been attracted to the investigation of this phenomenon. Landois,[15] in 1879, noticed that the recording obtained from a patient with aortic regurgitation differed from one obtained from a healthy person, in its waves of larger amplitude. Henderson,[12] for the first time in 1905, and later with Haldane and Douglas[7] on the Pikes Peak expedition, published his observations on the recordings and features of the "Recoil Curve of the Circulation as a Whole." Heald and Tucker,[11] in 1922, and Angenheister and Lau,[2] in 1928, reported on their methods of recording such motion.

Abramson,[1] in 1933, approached this problem with a knowledge of physical principles and obtained recordings from his subjects sitting on a chair with a spring mechanism. He was the first to develop a formula for calculating cardiac output; it later proved incorrect.

It was not until 1939, when Starr[28] published his paper reporting on the first organized and systematic study on this subject and giving the present-day accepted terminology, that the real interest in this field of investigation was aroused. Starr and his co-workers in their laboratory studied this problem from many points of view, including the significance and the value of amplitude for measurement of minute volume and the genesis and contour of the waves.

Over 300 papers have been published since in the medical literature. Among the most recent contributions are the excellent monographs of Brown and associates[3] and Dock and co-workers.[6] The scientific and ingenuous approach by various workers to improve, and yet to simplify, the instrumentation in order to

From the Department of Medicine, University of Ottawa, and Ottawa General Hospital, Ottawa, Canada.

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explore the value and limitations of this method of studying blood circulation in the body has stimulated the interest of the medical profession all over the world. In particular, the work and enthusiasm of Dock and Nickerson stand out in this respect.

During the last 15 years various studies pertaining to ballistocardiography as a method of determining cardiac abnormalities have been carried out. Since it was found wanting, a renewed interest in this technique was centered on the ballistocardiographic patterns, rather than on any other properties of the BCG, as an important tool in the diagnosis and prognosis of patients suffering from cardiovascular disorders. In spite of the fact that in the literature one could easily find conservative, skeptical, enthusiastic, and overenthusiastic opinions, the "ballistocardiogram" became popular to the point of reaching out even into the nonmedical press. In fact, Singewald,[23] in his lecture at the American College of Physicians in 1954, refers to an article in one such magazine which suggested "that a physical checkup could not be complete without a ballistocardiogram."

As has been stated, the ballistocardiogram is a record of body motion generated by the movements of the heart and the blood. It might appear, therefore, that it would be possible to estimate quantitatively the force of the heart from such records. However, because of several variables in the physical properties of the body, it is not possible to calculate accurately either the force of the heart or any other physical quantity. Consequently, it does not really matter what the BCG tracing actually represents physically, i.e., whether it is a displacement, velocity or acceleration curve. The problem, therefore, has to be tackled from the biologic viewpoint, i.e., normal patterns have to be established first, and then compared with those obtained in pathologic conditions. The following statements by Starr[26] and Dock[6b] are relevant to the present discussion. Starr stated, ". . . I doubt if any ballistocardiograph gives a completely true account of the forces which originate within the body and I shall cling to the simplest and most practical type and learn what I can from it," and ". . . I want to be able to answer the question whether the heart is strong or weak, and how well it is performing the function of pumping blood." Dock remarked, "Hence we differentiate our photoelectric signal, or integrate our electromagnetic signal, to yield what we have chosen to call a 'diagnostic' curve, midway between velocity and displacement. This is shocking to physicists, just as using beef heart as antigen in a test for syphilis is shocking to an immunologist. Our problem is clinical, not one of physics, and we do not intend to give up a method which has proved most valuable to us because it does not meet with the approval of someone who is not a clinician." For comparative purposes, then, as stated above, any type of ballistocardiograph is suitable, and for the investigations to be presented, Dock's electromagnetic "diagnostic" ballistocardiograph was selected because it is simple and economical enough for use in ordinary medical practice.

It should perhaps be mentioned that ballistocardiograms may be recorded in various planes (vertical, horizontal, and sagittal) using appropriate apparatus. The most popular method of recording is in the longitudinal axis, employing either indirect or direct recording machines. Indirect ballistocardiographs are based

on the principle of recording the movement of the top of a table mounted on springs; motion is imparted to the table top by the oscillating body. Direct ballistocardiographs record motions of the body lying on a fixed table. Dock's "diagnostic" ballistocardiograph belongs to the latter group and, as already stated, it does not record any particular physical property of the motion, in contrast to the ballistocardiographs belonging to the former group. Since no precise calculations are possible, in either case, the choice of the BCG type is a matter of taste and convenience.

In 1952, at the time of extreme divergence of opinion regarding the value of ballistocardiography, we became interested in the problem of its place in clinical medicine. We thought that since the ballistocardiogram furnished data hitherto unobtainable by other conventional methods of examination, it might help the physician in diagnosis and prognosis of cardiovascular diseases.

Consequently, for the purpose of estimating the clinical value of ballistocardiography, this study was divided into two parts: (1) the study of normal subjects and patients with cardiovascular diseases, in order to establish the conditions under which the ballistocardiograms should be recorded, and (2) the study of patterns obtained from normal subjects and from patients suffering from cardiovascular and other disorders, in order to determine the diagnostic and prognostic significance of ballistocardiograms by correlating them with clinical and laboratory data.

To attain the objectives of the first part of this study it was felt necessary to determine: (1) the usefulness of establishing a reference point by superimposing the QRS complex of the ECG on the ballistocardiogram; (2) the effect of such an imposition on the amplitude and pattern of the waves; (3) the effect of meals on the amplitude and pattern of the waves; and (4) the effect of routine physical activity on the amplitude and pattern of the waves.

Based on the study of 126 normal subjects of different age groups, and 127 patients suffering from cardiovascular and other disorders, the following conclusions were drawn: (1) In normal subjects neither daily routine activity, nor meals, nor superimposition of QRS complex affect specifically the amplitude or the pattern of the ballistocardiogram. (2) In patients suffering from various diseases the superimposition of QRS, and the time interval between the recording of the ballistocardiogram and the meals have no specific effect on the amplitude and the pattern of the ballistocardiogram; and 15 minutes' rest on the table in a number of cases resulted in producing an improved tracing as regards its pattern and amplitude.

Consequently, the following procedure in obtaining ballistocardiograms was considered advisable: (1) Two tracings, one after daily routine activity and the other after 15 minutes' rest, were taken without regard to meals or the time of the day. (2) The QRS was superimposed on the ballistocardiogram for the purpose of interpreting the waves.

METHOD AND MATERIAL

The method employed in the second part of this study was identical to that used in the first part.

TABLE I

Normal Subjects			115
Miscellaneous Group (comprising patients suffering from disorders other than those noted below)			265
Acute Upper Respiratory Infection			15
Primary Pulmonary Diseases			76
Bronchial Asthma		*15*	
Bronchiectasis		*5*	
Pulmonary Emphysema		*8*	
Chronic Exacerbated Bronchitis		*14*	
Bronchogenic Carcinoma		*10*	
Pneumonias (resolving)		*22*	
Bacterial	*17*		
Viral	*5*		
Pulmonary A-V Fistula (cong. telangiectasia)		*1*	
Empyema		*1*	
Diabetes Mellitus			30
Obesity (exogenous) Marked			6
Gall Bladder Diseases			13
Chronic Cholecystitis and Cholelithiasis		*9*	
Acute Cholecystitis		*2*	
Biliary Dyskinesia		*2*	
Diseases of Bones and Joints			19
Gouty Arthritis		*1*	
Rheumatoid Arthritis		*5*	
Osteoarthritis		*11*	
Paget's Disease of Bones		*2*	
Hypothyroidism			6
Thyrotoxicosis			3
Disorders of Blood			18
Purpuras (nonthrombocytopenic)		*2*	
Acute Leukemias		*2*	
Lymphosarcoma		*2*	
Chronic Leukemias		*2*	
Hodgkin's Disease		*2*	
Multiple Myeloma		*1*	
Pernicious Anemia		*7*	
Generalized Arteriosclerotic Vascular Disease (including Cerebral Thrombosis)			27
Arteriosclerotic Heart Disease (without decompensation)			43
Arteriosclerotic Heart Disease with Coronary Insufficiency (Angina Pectoris)			30
Coronary Arteriosclerotic Heart Disease with Thrombosis and Myocardial Infarction (healing stage)			20
Hypertensive Disease			32
Rheumatic Fever and Rheumatic Heart Disease			18
Active Rheumatic Fever		*7*	
Acute Pericarditis (without joint involvement)	*1*		
Aortic Incompetence	*1*		
Acute Rheumatic Fever (without valvular involvement)	*5*		
Inactive Phase with Chronic Valvular Disease		*11*	
Mitral Incompetence	*3*		
Mitral Stenosis	*4*		
Mitral and Aortic Regurgitation	*4*		
Congestive Heart Failure			62
Primary Disease			
Arteriosclerotic Heart Disease		*52*	
Chronic Rheumatic Valvular Disease		*5*	
Hypertensive Heart Disease		*3*	
Cor Pulmonale		*2*	
Total			798

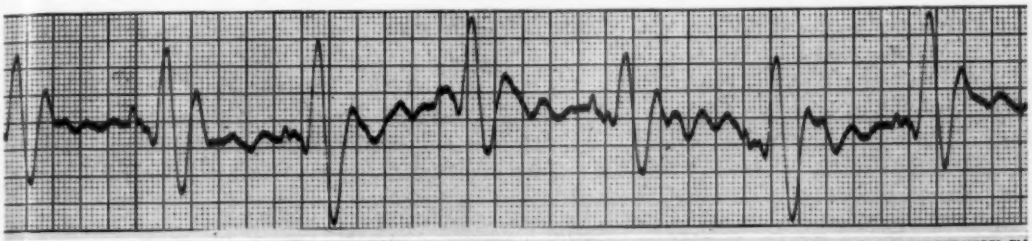

Fig. 1.

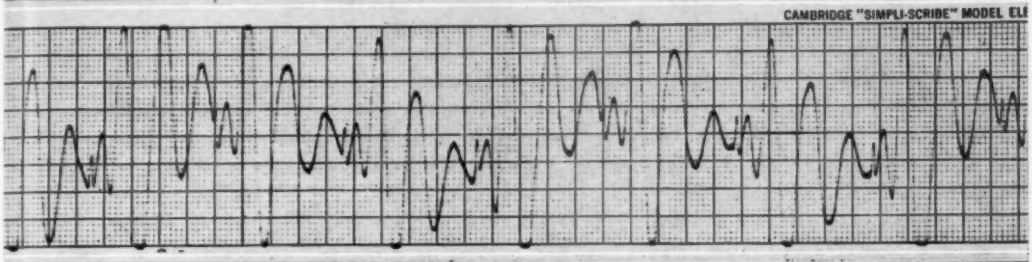

Fig. 2.

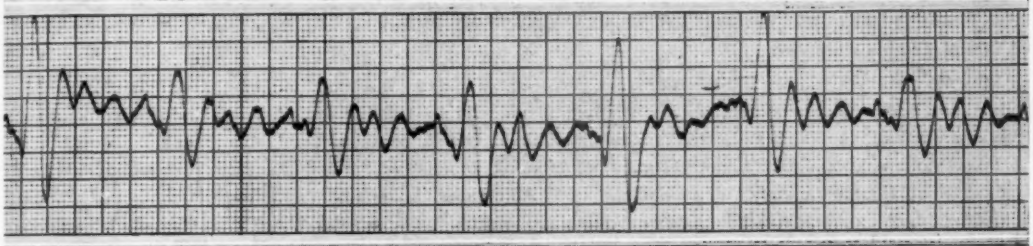

Fig. 3.

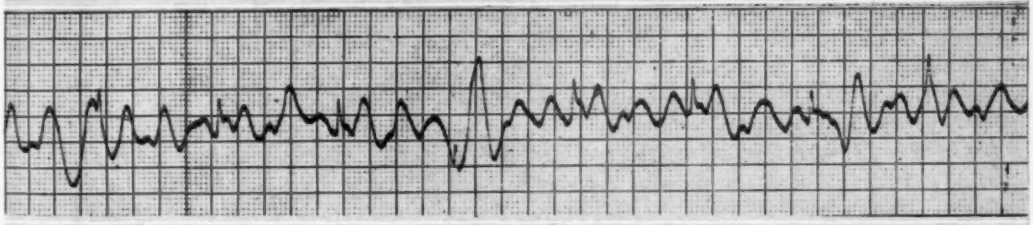

Fig. 4.

Fig. 5.

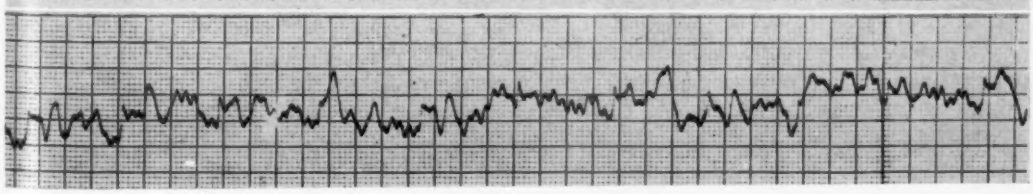

Fig. 6.

Fig. 1.—Normal tracing (Grade 0).
Fig. 2.—Normal tracing (Grade 0).
Fig. 3.—Grossly normal tracing (Grade I) but not quite of the same type as Grade 0.
Fig. 4.—Grossly normal tracing (Grade II) but further removed from the standard normal Grade 0 than Grade I.
Fig. 5.—Grossly abnormal tracing (Grade III).
Fig. 6.—Grossly abnormal tracing (Grade IV), more so than Grade III.

Although multichannel devices for simultaneous recording of the ballistocardiogram, the electrocardiogram, and/or the reference points like heart sound, pulse wave, etc., are available, it was felt that because of the expense involved they are of little practical value in office and ordinary hospital practice. Therefore, Dock's type direct body electromagnetic ballistocardiograph, consisting of a magnet holder, a foot rest, and a shin crosspiece with 2 coils and a 20 microfarad condenser,* and the Cambridge "Simpli-Scribe" direct-writing electrocardiograph as a recorder were selected. The subject lay on a heavy hardwood table with a small pillow under his head. Control tracings obtained on this table and on the floor showed no difference and no "extrabody" tremors.

It became apparent during the trial period that when the ECG instrument was adjusted to a standard sensitivity of 1 centimeter per millivolt, the amplitude of the tracings of certain subjects was greater than the width of the recording paper. This occurred especially in the younger age group. In order to overcome this difficulty and to avoid the necessity of adjusting the amplitude of the individual waves, an attempt was made to establish a uniform standardization. By trial and error this was obtained by adjusting the instrument to a sensitivity of 7 millimeters per millivolt.

The material studied was comprised of 115 normal subjects, and 683 patients suffering from various cardiovascular and other disorders. The subjects considered normal were those in whom no evidence of cardiovascular or any other disease was found on clinical, electrocardiographic, and radiologic examination.

Table I illustrates the distribution of the 683 patients according to their clinical diagnosis, priority being given to the diseases known to affect the cardiovascular system directly or indirectly. The miscellaneous group comprises various other disorders.

In order to study the short-term prognostic significance, repeat tracings on 347 of these patients were recorded, making a total of 1,637 ballistocardiograms.

For purpose of classifying these tracings the following gradings have been adopted:

Grade 0.—These are normal tracings with regard to amplitude and pattern. They are characterized by a J wave which is the highest and/or the more peaked wave of the complex; when the QRS component of the electrocardiogram is simultaneously recorded, the J wave follows the complex. It is preceded by a downward stroke—the I wave—and followed by another downward stroke—the K wave (Figs. 1 and 2).

Grade I.—These tracings are characterized by definitely identifiable waves with regular pattern. The amplitude of the shortest I-J waves is less than one third the amplitude of tallest I-J waves. Such abnormally short waves do not comprise more than 40 per cent of the total calculated on approximately 15 complexes (Fig. 3).

Grade II.—These tracings are characterized by small J, I, and K waves which are usually identifiable (Fig. 4).

Grade III.—These tracings are characterized by J waves which are sometimes unidentifiable, with I and/or K waves being absent. If these latter waves are present, they are of varying depth and/or shape (Fig. 5).

Grade IV.—These tracings have the same characteristics as those of Grade III, but their general pattern is completely irregular and bizarre (Fig. 6).

Similar gradings have been suggested by Brown[3] and Dock.[6] Although the above scheme is by no means without fault, and although in some tracings there is bound to be a certain overlapping, it was found useful, nevertheless, in the over-all analysis of the records.

RESULTS

The results of this study will be presented, first, under headings following as closely as possible the clinical classification of Table I and the BCG gradings enumerated above. Secondly, comparisons will be made (1) between the normal group and the group having diseases known not to affect the cardio-

*Made by Everett M. Hill, Ellsworth, Maine.

vascular system; (2) between diseases which may affect the cardiovascular system; and (3) between the diseases which do affect the cardiovascular system, in order to find out whether there are any significant differences. If such differences

TABLE II. NORMAL SUBJECTS

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19	19	100									19
20–29	64	98			1	1.4					65
30–39	11	61	1	5	4	22	2	11			18
40–49	1	14			6	86					7
50–59	1	20	1	20	2	40	1	20			5
60–69											
70–79							1				1
80–89											
90–99											
Total	96	83	2	1.7	13	11	4	3.5			115

In groups comprised of fewer than 5 subjects percentages are not calculated.

TABLE III. PATIENTS WITH MISCELLANEOUS DISORDERS

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19	17	100									17
20–29	26	74	1	3	5	14	3	9			35
30–39	25	62			13	32	1	2.5	1	2.5	40
40–49	16	30			25	47	12	23			53
50–59	12	29			13	31	14	34	2	5	41
60–69	4	10	1	3	18	46	13	33	3	7	39
70–79					16	43	18	50	3	7	37
80–89	1								1		2
90–99							1				1
Total	101	38	2	0.7	90	34	62	23	10	4	265

are not found, the whole material will be divided into three major groups: a normal group (Group 1), a group with diseases which may affect the cardiovascular system (Group 2), and a group with diseases which does affect it (Group 3). Third, for clarity of presentation, stress will be laid on grossly normal ballisto-

TABLE IV. MAJOR CLINICAL GROUP 1 (COMBINED NORMAL AND MISCELLANEOUS GROUPS OF TABLES II AND III)

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19	36	100									36
20–29	90	90	1	1	6	6	3	3			100
30–39	36	63	1	2	17	29	3	6	1	2	58
40–49	17	28			31	51	12	2			60
50–59	13	28	1	2	15	32	15	32	2	4	46
60–69	4	10	1	2	18	46	13	33	3	8	39
70–79					16	42	19	50	3	8	38
80–89	1								1		2
90–99							1				1
Total	197	52	4	1	103	27	66	17	10	2.6	380

TABLE V. PATIENTS WITH ACUTE UPPER RESPIRATORY INFECTION

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19	4										4
20–29	1										1
30–39	1										1
40–49					1						1
50–59					3						3
60–69							1				1
70–79			1		1						2
80–89							2				2
90–99											0
Total	6	40	1	6	5	33	3	20			15

cardiograms, i.e., those of Grades 0, I, and II, and grossly abnormal ballistocardiograms, i.e., those of Grades III and IV. Thus, our final discussion will be concerned with three major clinical groups and two major ballistocardiographic divisions. From the technical point of view, the data for each disease or major

TABLE VI. PATIENTS WITH ACUTE AND/OR CHRONIC PULMONARY DISEASES

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19	3										3
20–29	3										3
30–39	6	66	1	11	1	11	1	11			9
40–49	2	33			2	33	2	33			6
50–59	2	13	2	13	5	33	5	33	1	7	15
60–69	3	14	2	9	7	32	8	36	2	9	22
70–79			2	13	3	20	9	60	1	7	15
80–89							3				3
90–99											0
Total	19	25	7	9	18	23	28	37	4	5	76

TABLE VII. PATIENTS WITH DIABETES MELLITUS

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19	2										2
20–29	1										1
30–39	1										1
40–49	1	20			3	60			1	20	5
50–59					3	33	6	66			9
60–69					3	50	3	50			6
70–79							4	66	2	33	6
80–89											
90–99											
Total	5	16			9	30	13	43	3	10	30

group, will be presented in a table, with arrangement of the data according to age and BCG grading (Tables II-XXIV). These results are based on the study of the second tracing, i.e., after the subject had had approximately 15 minutes' rest on the table. The distribution of the ballistocardiograms according to age and sex has been omitted, because it does not provide any additional information.

TABLE VIII. PATIENTS WITH EXOGENOUS OBESITY

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19	1										1
20–29					1						1
30–39											0
40–49							1				1
50–59											0
60–69	1						1				2
70–79	1										1
80–89											0
90–99											0
Total	3	50			1	16	2	33			6

TABLE IX. PATIENTS WITH GALLBLADDER DISORDERS

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19											0
20–29											0
30–39	1										1
40–49	1				2						3
50–59					1		1				2
60–69					2		2				4
70–79					2		1				3
80–89											0
90–99											0
Total	2	16			7	54	4	30			13

Table II shows data obtained in normal people, and Table III data from the miscellaneous group, i.e., from a group of patients with disorders which are known not to affect the cardiovascular system. Taking into account the small number of cases in each age group, comparison of these two tables does not show

TABLE X. PATIENTS WITH ARTHRITIS (VARIOUS FORMS) AND PAGET'S DISEASE OF BONE

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19											0
20–29	1						1				2
30–39											0
40–49					1						1
50–59	1	20			2	40	2	40			5
60–69					2	40	3	60			5
70–79					1		2		1		4
80–89					1		1				2
90–99											0
Total	2	11			7	37	9	47	1	5	19

TABLE XI. PATIENTS WITH HYPOTHYROIDISM

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19	1										1
20–29							1				1
30–39	1										1
40–49											0
50–59					1		1				2
60–69					1						1
70–79											0
80–89											0
90–99											0
Total	2	33			2	33	2	33			6

any substantial statistical difference. Thus, it seems justifiable to combine these two groups into one major group of normal people (Group 1). Table IV presents the amalgamated results of this major group.

Tables V to XIII contain data obtained in patients with disorders which may affect the cardiovascular system. Comparison of these tables, if once again

TABLE XII. PATIENTS WITH HYPERTHYROIDISM

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19											
20–29											
30–39							1				1
40–49			1								1
50–59							1				1
60–69											
70–79											
80–89											
90–99											
Total			1	0			2	0			3

TABLE XIII. PATIENTS WITH ANEMIAS AND LYMPHOMAS

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19											
20–29	1										1
30–39											
40–49	1				1						2
50–59	2	40	1	20	2	40					5
60–69	2				1						3
70–79					4	66	2	33			6
80–89							1				1
90–99											
Total	6	33	1	6	8	44	3	17			18

an allowance is made for the statistically small number of cases in each group, does not show any substantial difference. Therefore, the data of these tables have been combined in Table XIV to form Group 2, i.e., a group composed of patients having various diseases which may affect the cardiovascular system. It

TABLE XIV. MAJOR CLINICAL GROUP 2 (COMBINED TABLES V–XIII)

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19	11	100									11
20–29	7	70			1	10	2	20			10
30–39	10	71	1	7	1	7	2	14			14
40–49	5	25	1	5	10	50	3	15	1	5	20
50–59	5	12	3	7	17	40	16	38	1	2	42
60–69	6	14	2	4.5	16	36	18	40	2	4.5	44
70–79	1	2.5	3	8	11	30	18	49	4	11	37
80–89					1	12	7	88			8
90–99											0
Total	45	24	10	5	57	30	66	36	8	5	186

TABLE XV. PATIENTS WITH GENERALIZED ARTERIOSCLEROTIC VASCULAR DISEASE (INCLUDING CEREBRAL THROMBOSIS)

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19											
20–29											
30–39											
40–49											
50–59							1				1
60–69					3	43	4	57			7
70–79	2	13			4	27	7	47	2	13	15
80–89							2		2		4
90–99											
Total	2	7			7	26	14	52	4	15	27

may be noted, in passing, that in patients with anemias and lymphomas (Table XIII) not a single Grade IV tracing was recorded, a lead which perhaps might be worth following.

Once again, since the comparison of the data of Tables XV through XXIII does not reveal marked differences, they have been combined into the third

TABLE XVI. ARTERIOSCLEROTIC HEART DISEASE (WITHOUT DECOMPENSATION)

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19											
20–29											
30–39											
40–49											
50–59					2				1		3
60–69			1	9	3	27	5	45	2	18	11
70–79			1	5	3	14	12	56	5	24	21
80–89					2	25	3	37	3	37	8
90–99											
Total			2	5	10	23	20	47	11	25	43

TABLE XVII. CORONARY ARTERIOSCLEROSIS WITH INSUFFICIENCY (ANGINA)

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19											
20–29											
30–39											
40–49					1		2				3
50–59			1	10	2	20	3	30	4	40	10
60–69							5	45	6	55	11
70–79							1		3		4
80–89							1		1		2
90–99											
Total			1	3	3	10	12	40	14	47	30

major clinical group in Table XXIV. This Group 3 is comprised of patients having definite disorders of the cardiovascular system. However, it should be noted that the group having arteriosclerotic heart disease with angina (Table XVII), and the group having arteriosclerotic heart disease with myocardial infarction

TABLE XVIII. CORONARY ARTERIOSCLEROSIS WITH MYOCARDIAL INFARCTION (HEALING STAGE)

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19											
20–29											
30–39									1		1
40–49							1		1		2
50–59			1				1		2		4
60–69									4		4
70–79							1	11	8	89	9
80–89											
90–99											
Total			1	5			3	15	16	80	20

TABLE XIX. HYPERTENSIVE DISEASE

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19											
20–29											
30–39	1				1						2
40–49			1	16	4	67	1	16			6
50–59	1	10			1	10	8	80			10
60–69			2	25	2	25	4	50			8
70–79					2	33	4	66			6
80–89											
90–99											
Total	2	6	3	9	10	31	17	54			32

(Table XVIII) show more abnormalities than either the group with generalized arteriosclerosis (Table XV) or the group having arteriosclerotic heart disease without angina or cardiac infarct (Table XVI). In fact, it may be stated that the generalized arteriosclerotic group, together with the arteriosclerotic heart disease group, on the one hand, and the anginal group with myocardial infarct group, on the other, are representative of the mildest and severest abnormalities in this Group 3. Groups with the other diseases lie between these two extremes.

TABLE XX. ACTIVE RHEUMATIC FEVER

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
1–9	1										1
10–19	4	80			1	20					5
20–29			1								1
30–39											
40–49											
50–59											
Total	5	71	1	14	1	14					7

TABLE XXI. CHRONIC RHEUMATIC VALVULAR DISEASES

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19	1										1
20–29							1				1
30–39	1						2				3
40–49	1				1		1		1		4
50–59	1										1
60–69							1				1
70–79											
80–89											
90–99											
Total	4	37			1	9	5	45	1	9	11

However, the differences are not great, a not so surprising fact since the BCG is presumably the reflection of the function of the cardiovascular system, which may be affected in the same manner by various structural abnormalities.

TABLE XXII. ARTERIOSCLEROTIC HEART DISEASE WITH CONGESTIVE HEART FAILURE

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19											
20–29											
30–39											
40–49					1		1				2
50–59	1	12			4	50	3	38			8
60–69					3	20	9	60	3	20	15
70–79	1	4	2	8	2	8	13	54	6	25	24
80–89					2		1				3
90–99											
Total	2	4	2	4	12	23	27	52	9	17	52

TABLE XXIII. PATIENTS WITH CONGESTIVE HEART FAILURE DUE TO DISORDERS OTHER THAN ARTERIOSCLEROTIC HEART DISEASE

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19											
20–29											
30–39					1		1				2
40–49			1	20			3	60	1	20	5
50–59							1		1		2
60–69					1						1
70–79											
80–89											
90–99											
Total			1	10	2	20	5	50	2	20	10

TABLE XXIV. MAJOR CLINICAL GROUP 3 (COMBINED TABLES XV-XXIII)

AGE (YEARS)	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
1–9	1										1
10–19	5	83			1	17					6
20–29			1				1				2
30–39	2	25			2	25	3	38	1	12	8
40–49	1	4.5	2	9	7	32	9	41	3	14	22
50–59	3	8	2	5	9	23	17	43	8	20	39
60–69			3	5	12	20	28	48	15	26	58
70–79	3	4	3	4	11	14	38	48	24	30	79
80–89					4	23	6	35	7	41	17
Total	15	6	11	4	46	20	102	44	58	25	232

DISCUSSION

We have tailored our material into three main clinical groups: normal Group 1 (Table IV); Group 2, with diseases which may affect the cardiovascular system (Table XIV); and Group 3, with diseases which do affect the cardiovascular system (Table XXIV).

To facilitate comparison among these groups, Tables XXV and XXVI were constructed. In the latter table the youngest and the oldest age group were eliminated because of the small number of cases, and the material was condensed into three major age groups in order to emphasize certain points.

The perusal of these tables, and particularly Table XXV, shows that, generally speaking, in each age group the number of abnormal ballistocardiograms increases and the number of normal ballistocardiograms decreases as one passes from Group 1, through Group 2, to Group 3. However, there are exceptions. For example, in Table XXVI the percentage of Grade II ballistocardiograms in the age group 40-59 diminishes rather than increases, and in the same table the number of normal ballistocardiograms in the age group 60-79 increases in Group 2. The same may be said about some other tables. For example, in Table II the incidence of Grade II ballistocardiograms in the age group 40-49 is greater than in the older age groups. Some of these discrepancies may be explained on statistical grounds since our groups are rather small. However, other factors may also play a part. It may be argued that these variations are due to incorrect clinical assessment of the patients or to the possibility that the ballistocardiogram does not represent the function of the cardiovascular system. Since these two possibilities are unlikely, the following one may explain these discrepancies more satisfactorily. It is to be noted that the examples pointed out concern either

Grade 0, I, or II of the ballistocardiogram, i.e., ballistocardiograms whose patterns are not very much dissimilar. If the ballistocardiograms are classified into grossly normal (Grade 0, I, and II) and grossly abnormal (Grade III and IV), these discrepancies would disappear. Such an attempt is made in Table XXVII, which shows the general trend more clearly, and in which there are no longer any discrepancies. This observation may be used in favor of the argument that the classification of the ballistocardiograms into the two divisions "grossly normal" and "grossly abnormal" is sufficient for the present clinical purposes.

It has been surmised in the literature that abnormal ballistocardiograms are suggestive of myocardial impairment even in people who on clinical grounds are considered normal.[6,6a,16,22,25,27] This suggestion was made on the basis that the incidence of abnormal ballistocardiograms increases with age, as does coronary sclerosis, and that a higher percentage of certain people with abnormal ballistocardiograms develops heart diseases when followed for a number of years.

The material of the present study is not suitable for discussion of the latter point, and only further, more extensive investigations could answer the question posed by it. However, the former supposition deserves some comment.

Analysis of Table IV shows that the number of abnormal ballistocardiograms increases with age, and it appears from Tables XXV, XXVI, and XXVII that apart from age, which in such a comparison is eliminated, changes in the cardiovascular system contribute to the BCG abnormality. It may be argued, therefore, that these abnormalities in older groups of Group 1 may be attributed to the changes in the cardiovascular system rather than to other factors.

However, this argument, that the increased incidence of abnormal ballistocardiograms in the group with cardiovascular disorders could be used in favor of the assertion that all abnormal ballistocardiograms, even in the group classified on clinical grounds as normal, should be indicative of abnormalities in the cardiovascular system, is not quite valid because to assert this would be tantamount to saying that cases classified as normal were in reality abnormal. Conversely one might assert on the same grounds that since the incidence of normal ballistocardiograms in the normal group is higher than in the group with cardiovascular disorders, cases with cardiovascular abnormalities detectable on clinical grounds should be considered normal. Thus, the whole argument narrows down to the assertion that classification on clinical grounds is invalid and that ballistocardiograms alone should serve as the basis for classification. Since, as has been stated, the ballistocardiogram does not reflect cardiovascular forces alone, such an assertion cannot be made at the present time. Consequently, the increased incidence of BCG abnormalities in the group with cardiovascular disorders may only draw one's attention to the possibility of changes in this system.

The collateral argument, drawn from pathologic observations, that the incidence of myocardial changes and coronary arteriosclerosis increases with age and that, therefore, these conditions may be present in people who do not give clinical evidence of them would also assert that clinical classification is erroneous and that people of older age in the normal group therefore should be classified as abnormal. Since it is impossible to classify living people on this basis, this argument loses much of its force.

This type of reasoning applies not only to the present problem, but also to many other clinical studies of similar type. For example, there was a time when the Wassermann reaction and other serologic reactions were considered almost specific for syphilis; this was based on a correlation similar to the one presented here. Only recently has the possibility of false positive biologic reactions gained

TABLE XXV. COMPARISON OF THE THREE MAJOR CLINICAL GROUPS

AGE (YEARS)	GROUP	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
10–19	1	36	100	0	0	0	0	0	0	0	0	36
	2	11	100	0	0	0	0	0	0	0	0	11
	3	5	84	0	0	1	16	0	0	0	0	6
20–29	1	90	90	1	1	6	6	3	3	0	0	100
	2	7	70	0	0	1	10	2	20	0	0	10
	3	0	0	1	0	0	0	1	0	0	0	2
30–39	1	36	63	1	2	17	29	3	6	1	2	58
	2	10	71	1	7	1	7	2	14	0	0	14
	3	2	25	0	0	2	25	3	38	1	12	8
40–49	1	17	28	0	0	31	51	12	20	0	0	60
	2	5	25	1	5	10	50	3	15	1	5	20
	3	1	4.5	2	9	7	32	9	41	3	14	22
50–59	1	13	28	1	2	15	32	15	32	2	4	46
	2	5	12	3	7	17	40	16	38	1	2	42
	3	3	8	2	5	9	23	17	43	8	20	39
60–69	1	4	10	1	2	18	46	13	33	3	8	39
	2	6	14	2	4.5	16	36	18	40	2	4.5	44
	3	0	0	3	5	12	20	28	48	15	26	58
70–79	1	0	0	0	0	16	42	19	50	3	8	38
	2	1	2	3	8	11	30	18	49	4	11	37
	3	3	4	3	4	11	14	38	48	24	34	79
80–89	1	1	0	0	0	0	0	0	0	1	0	2
	2	0	0	0	0	1	12	7	88	0	0	8
	3	0	0	0	0	4	23	6	35	7	41	17

In groups comprised of fewer than 5 subjects percentages are not calculated.

much wider acceptance, so that a positive serologic reaction is an indication for a more intensive study of the case rather than a diagnosis in itself. As a matter of fact, all studies based on a correlation of clinical findings with a new method of examination may be summed up thus: A group of skilled workers (or a skilled worker) has established the diagnosis on clinical grounds after a thorough examination and correlated these diagnoses with a new method of examination. They have found that this correlation in certain groups is fairly high and in other groups fairly low. Hence a conclusion is drawn that this method of examination would be of help in diagnosis of certain conditions. As a matter of fact, for this group of workers this new test is in reality unnecessary because they know a priori on clinical grounds what the diagnosis is. However, the test may have a certain value for other, less skilled workers, drawing their attention to the necessity of performing a more thorough examination. But the whole trouble starts

TABLE XXVI. COMPARISON OF THREE MAJOR CLINICAL GROUPS EXCLUSIVE OF THE YOUNGEST AND OLDEST AGE GROUPS AND CONDENSED INTO THREE MAJOR AGE GROUPS

AGE (YEARS)	CLINICAL GROUP	GRADE 0		GRADE I		GRADE II		GRADE III		GRADE IV		TOTAL
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
20–39	1	126	80	2	1	23	14	6	4	1	0.7	158
	2	17	71	1	4	2	8	4	17	0	0	24
	3	2	20	1	10	2	20	4	40	1	10	10
40–59	1	30	28	1	1	46	43	27	25	2	2	106
	2	10	16	4	6	27	43	19	30	2	3	62
	3	4	6	4	6	16	26	26	42	11	20	61
60–79	1	4	5	1	1	34	44	32	40	6	8	77
	2	7	8	5	6	27	33	36	44	6	8	81
	3	3	2	6	4	23	17	66	50	39	27	137

TABLE XXVII. COMPARISON OF THREE MAJOR CLINICAL GROUPS AND TWO MAJOR BCG GRADES

CLINICAL GROUP	AGE (YEARS)	GROSSLY NORMAL BALLISTOCARDIOGRAM (GRADES 0, I, II)		GROSSLY ABNORMAL BALLISTOCARDIOGRAM (GRADES III AND IV)		TOTAL NO. OF CASES
		NO.	%	NO.	%	
1	20–39	151	95.6	7	4.4	158
	40–59	20	83	4	17	24
	60–79	5	50	5	50	10
2	20–39	77	72.6	29	27.4	106
	40–59	41	66	21	34	62
	60–79	24	39.3	37	60.7	61
3	20–39	39	50.6	38	49.4	77
	40–59	39	48	42	52	81
	60–79	32	23.3	105	76.7	137

when such a test is used interchangeably with clinical diagnosis, i.e., when it is assumed that this correlation is exactly 100 per cent. Since such correlation does not exist, the value of each new method has to be based on the degree of probability which it contributes to the solution of the problem. In order then to assess the value of ballistocardiography in clinical diagnosis, a correlation between clinical groups and BCG gradings is presented in Table XXVIII.

TABLE XXVIII. CORRELATION BETWEEN THREE MAJOR CLINICAL GROUPS AND TWO MAJOR BCG GRADINGS

BCG GRADES	AGE GROUP (YEARS)								
	20–39			40–59			60–79		
	GROUP 1	GROUP 2	GROUP 3	GROUP 1	GROUP 2	GROUP 3	GROUP 1	GROUP 2	GROUP 3
(0-I-II)	86%	11%	3%	50%	33%	17%	36%	34%	30%
(III-IV)	44%	25%	31%	33%	24%	43%	20%	24%	56%

Comparison of the normal group with the group having cardiovascular abnormalities shows that a grossly normal ballistocardiogram in the age group 20-39 is suggestive of a normally functioning cardiovascular system; in the age group 40-59 it may still be considered as an argument in favor of a normally functioning cardiovascular system; and in the age group 60-79 it may or may not be so considered. It may be seen also from this table that a grossly abnormal ballistocardiogram in the age group 20-39 may or may not be suggestive of a normally functioning cardiovascular system; and in the age groups 40-59 and 60-79 it is rather indicative of malfunctioning of this system. In the miscellaneous group the clinical examination showed that the cardiovascular system was definitely normal, but since many of the conditions included in the miscellaneous category are known to affect the cardiovascular system, it is reasonable to suppose that at least some cases in this group had cardiovascular dysfunction. Consequently, the value of ballistocardiography in clinical practice seems to be as follows: *A grossly normal ballistocardiogram* in the age group 20-39 may be taken as an argument in favor of a normally functioning cardiovascular system; in the age group 40-59 it may still be taken as signifying a normally functioning cardiovascular system; and in the age group 60-79 it may or may not reflect normal function. *A grossly abnormal ballistocardiogram* in the age group 20-39 may or may not be indicative of a normally functioning cardiovascular system; and in the age group 40-59, and particularly in the age group 60-79, it is in favor of malfunctioning of the cardiovascular system.

Various claims have been made as to the diagnostic value of the ballistocardiogram in certain congenital and acquired cardiovascular disorders. Of all such conditions associated with ballistic patterns, and one considered to be characteristic, coarctation of the aorta has been mentioned most commonly. Hamilton,[10] in 1945, described the shallow K wave occurring in this anomaly. This

finding has been confirmed subsequently by various workers.[4,20] Typically, the K wave in most of the patients has been found to terminate sharply much above the base line. Nickerson and his associates[20] have further shown the reappearance of a normal K wave following surgical correction of the coarctation. However, since "forces" responsible for such an abnormal K wave are dependent on constriction of the aorta, similar patterns would be expected in aortic occlusion due to thrombosis. Such cases with shallow K wave and with improvement following surgical treatment of aortic thrombosis have been described.[7a] However, the matter is further complicated by the finding of such characteristic tracings in some normal people and in patients with shock.[6]

In other congenital heart diseases, the information regarding the BCG patterns is rather meager. Dock[6] mentions low amplitude of waves in cases with pure pulmonic stenosis. Frankel and Rothermich[8] describe a very deep H-I and I-J slope in a patient diagnosed, and confirmed on thoracotomy, as having pure pulmonic stenosis. The latter authors also noted a tall L and a broad J peak in a case of ventricular septal defect.

In thyrotoxicosis large amplitude waves have been seen. Because of increased cardiac output this is not surprising, and Mathers and associates[17] stress the point that such tracings are found so consistently in these patients that their absence should make one suspicious of the diagnosis.

Various types of BCG patterns have been described in acquired valvular lesions. Small I waves, notching and slurring of I-J segments, tall L and N waves, and "bowing" and "angulation" of J-K segments have all been mentioned as characteristic of one or another abnormality. Davis[5] observed in pure mitral stenosis a wave preceding the I wave and referred to it as "doubling of I."

Dock[6] described diminished respiratory variations of the J wave and lack of its increased amplitude on exercise, and regards these changes as signifying an absence of significant mitral insufficiency. Brown[3] mentioned tall L and N waves in some cases of mitral stenosis. Kuo and Schnabel[14] observed an additional positive systolic wave interspersed between the I and J waves.

Despite all the foregoing observations, Newman[19] failed to notice any change in BCG patterns in experimentally produced mitral insufficiency. Izak and Braun,[13] in a study of 44 mitral cases, found no specific BCG pattern that could help to differentiate mitral stenosis from mitral insufficiency. Neither could they demonstrate significant correlation of various hemodynamic data with ballistic waves. However, they consider BCG changes before and after valvulotomy as a helpful method for evaluation of clinical improvement.

In aortic insufficiency large amplitude waves have been reported. Smith[24] found the acceleration ballistocardiogram more valuable in this condition and described the higher amplitude of K and notching of J with the I:K ratio over 1.3. Van Lingen,[29] using a low-frequency critically-damped ballistocardiograph, demonstrated the "outward bowing" or increased "angulation" of J-K in cases with aortic stenosis. A smaller "angulation" of J-K may be seen occasionally in other disorders but a tendency of this "angulation" to become accentuated in deep inspiration is considered a characteristic feature of pure aortic stenosis.

The review of the literature, then, appears to indicate that there are no definite diagnostic patterns, an opinion expressed also by Pollock.[21]

We had no experience with some of the aforementioned conditions, and no definite judgment is possible, therefore, as far as they are concerned. However, it seems from this study that since various structural abnormalities may produce the same pattern, and since the ballistocardiogram is the reflection of function rather than structure, it is unlikely that the BCG could be used profitably in the diagnosis of structural lesions. The value of ballistocardiography, like that of any other laboratory procedure, appears to be limited, but it might tip the balance in doubtful cases if used judiciously, and in conjunction with other methods of examination.

REFERENCES

1. Abramson, E.: Skandinav. Arch. f. Physiol. **66**:191, 1933. Referred to in Brown, H. R., Jr.[3]
2. Angenheister, G., and Lau, E.: Naturwissenschaften **16**:513, 1928. Referred to by Starr, I.: J.A.M.A. **155**:1413, 1954.
3. Brown, H. R., Jr., deLalla, V., Jr., Epstein, M. A., and Hoffman, M. J.: Clinical Ballistocardiography, New York, 1952, The Macmillan Company.
4. Brown, H. R., Jr., Hoffman, M. J., and deLalla, V., Jr.: New England J. Med. **240**:715, 1949.
5. Davis, F. W., Jr., Scarborough, W. R., Mason, R. E., Singewald, M. L., and Baker, B. M., Jr.: Circulation **7**:503, 1953.
6. Dock, W., Mandelbaum, H., and Mandelbaum, R. A.: Ballistocardiography, St. Louis, 1953, The C. V. Mosby Company.

6a. Ibid. p. 147.

6b. Ibid. p. 244.

7. Douglas, C. G., Haldane, J. S., Henderson, Y., and Schneider, E. C.: Trans. Roy. Soc. (London), Series B **203**:185, 1913. Referred to by Brown.[3]

7a. Elkins, D. C., and Cooper, F. W.: Ann. Surg. **130**:417, 1949.

8. Frankel, A. L., and Rothermich, N. O.: Ann. Int. Med. **36**:1385, 1952.
9. Gordon, J. W.: J. Anat. & Physiol. **11**:533, 1877.
10. Hamilton, W. J., Remington, J. W., and Dow, P.: Am J. Physiol. **144**:555, 1945.
11. Heald, C. D., and Tucker, W. S.: Proc. Roy. Soc. (London), Series B **93**:281, 1922.
12. Henderson, Y.: Am. J. Physiol. **14**:287, 1905.
13. Izak, J., and Braun, K.: Brit. Heart J. **18**:44, 1956.
14. Kuo, P. T., and Schnabel, T. G.: Am. J. Med. **15**:50, 1953.
15. Landois, L.: Lehrbuch der Physiologie des Menschen, Vienna, 1879, Urban und Schwarzenberg. Referred to by Starr, I.: J.A.M.A. **155**:1413, 1954.
16. Master, A. M., Donoso, E., Pordy, L., and Chesky, K.: Am. Heart J. **46**:180, 1953.
17. Mathers, J. A. L., Nickerson, J. L., Fleming, T. C., and Patterson, M. C.: Am. Heart J. **40**:390, 1950.
18. Murphy, R. A.: Am. Heart J. **39**:174, 1950.
19. Newman, M. M., Bay, E. B., and Adams, W. E.: Am. J. Physiol. **165**:497, 1951.
20. Nickerson, J. L., Humphrey, G. H., Deterling, R. A., Fleming, T. C., and Mathers, J. A. L.: Circulation **1**:1032, 1950.
21. Pollock, P.: Canad. M.A.J. **76**:778, 1957.
22. Scarborough, W. R., Mason, R. E., Davis, F. W., Jr., Singewald, M. L., Baker, B. M., Jr., and Lore, S. A.: Am. Heart J. **44**:645, 1952.
23. Singewald, M. L.: Ann. Int. Med. **41**:1124, 1954.
24. Smith, J. E., Rosenbaum, R., and Ostrich, R.: Am. Heart J. **48**:847, 1954.
25. Starr, I.: Am. J. M. Sc. **214**:233, 1947.
26. Starr, I.: The Harvey Lectures, Series 42, 1946-1947, pp. 194-219.
27. Starr, I., and Hildreth, E. A.: Circulation **5**:481, 1952.
28. Starr, I., Rawson, A. J., Schroeder, H. A., and Joseph, N. R.: Am. J. Physiol. **127**:1, 1939.
29. Van Lingen, B., Gear, J. R., Whidborne, J., and Lister, M. L.: Am. Heart J. **47**:560, 1954.

Pitfalls in the Diagnosis of Pulmonary Hypertension

Jonas Brachfeld, M.D., Attilio Reale, M.D.,** and Harry Goldberg, M.D.*
Philadelphia, Pa.

In spite of increasing interest in primary pulmonary hypertension,[1-4] the nature of this condition remains obscure. The clinical picture is entirely nonspecific. This syndrome may be properly included in the differential diagnosis of the patient who presents evidence of right ventricular hypertrophy and/or pulmonary hypertension. Clinically, the syndrome may occur in all age groups but is found most commonly in young adults; some series comprise a large proportion of females.[2] Its course may be fulminant or may run for years. The symptoms are equally nonspecific. There may be a history of weakness or general malaise; severe dyspnea on effort is often a presenting complaint, and is characteristically not associated with orthopnea. Dyspnea at rest occurs late in the disease. Hoarseness, or chest pain simulating angina may lead to the detection of a dilated pulmonary artery, and prompt further study. Syncope on effort and sudden death, especially after trivial surgical procedures, may be the only manifestations. Hemoptysis is rare.[4] Right heart failure and peripheral cyanosis are frequently seen in the end stages.

In the typical case there is a palpable heave over the pericardium, an accentuated second pulmonic sound, and a systolic murmur to the left of the sternum. Roentgenograms confirm the presence of prominent right ventricular and pulmonary artery salients; the pulmonary hilar vessels are increased in size while the peripheral lung fields show decreased vascularity. The left atrium and the pulmonary parenchyma appear normal. The electrocardiogram shows right ventricular hypertrophy. With such findings, the presence of sinus rhythm, the absence of notching of the P waves, and the presence of tall peaked P waves are suggestive of pulmonary hypertension due to lung disease, left-to-right shunt or primary pulmonary hypertension rather than mitral stenosis. However, none of these signs are reliable. The following variants have been encountered: The systolic murmur may be absent. This murmur is usually attributed to dilatation of the pulmonary artery and/or relative pulmonary stenosis, but may actually

From the Brith Sholom Cardiopulmonary Laboratory and the Department of Medicine, Hahnemann Medical College and Hospital, and the Bailey Thoracic Clinic, Philadelphia, Pa.
Received for publication Jan. 7, 1958.
*Work done during tenure of National Heart Institute Traineeship.
**Present address is 24 Via Archimede, Rome, Italy.

be due to tricuspid insufficiency (Case 3). Its location may vary; it may be heard best at the upper or at the lower part of the left sternal border, or even at the apex. An early diastolic murmur may be heard, due to pulmonary insufficiency. A mid-late diastolic rumble (relative tricuspid stenosis) at the apex or to the left of the sternum may be particularly misleading (Case 2). The roentgenograms may be normal. They may show engorged rather than oligemic peripheral fields. The size of the left atrium is difficult to estimate in the rare case where there is marked generalized cardiac enlargement. The electrocardiogram may be normal or atrial fibrillation may be recorded occasionally.[4]

One cause for the difficulties in defining a definite syndrome of primary pulmonary hypertension may be the manner in which the cases have been collected. Earlier series were presented by pathologists who collected instances of right ventricular hypertrophy and/or pulmonary arteriosclerosis without apparent cause. Many of these cases, collected from autopsies performed at a time when the influence of intracardiac shunts was not fully appreciated, may have represented small, high ventricular septal defects or other lesions.[6,7] Pulmonary-bronchial arterial shunts are particularly likely to escape detection. More recent series have come from cardiopulmonary laboratories, where pulmonary hypertension was found on catheterization but no cause could be demonstrated by physiologic methods. Dresdale's[8] cases seemed to fit best into a single syndrome. However, this very fact, and the favorable response to Priscoline which he observed, perhaps suggest that he studied one particular, but as yet undefined, modality of primary pulmonary hypertension.

In the absence of a clearly defined syndrome, rigorous criteria must be fulfilled before a case can be accepted as one representing primary pulmonary hypertension. This is not only of academic interest, but it may ultimately shed light on the general problem of pulmonary hypertension and the factors influencing its development, course, and therapy. For example, some of the reported cases in which Priscoline failed to lower the pulmonary pressure may not have represented "primary" pulmonary hypertension. Known causes of pulmonary hypertension which must be ruled out before one is left with the latter may be classified as follows:

1. *Diseases of Pulmonary Parenchyma.*—Diseases of the pulmonary parenchyma include pulmonary agenesis, cysts, extensive pulmonary emphysema and fibrosis, granulomas (sarcoid, berylliosis, miliary tuberculosis), carcinoma of the lung, and Hamman-Rich syndrome. Theoretically, pulmonary function studies should be performed to rule out the presence of parenchymal lung disease when one is confronted with pulmonary hypertension of unknown etiology. In practice it is unlikely that such a diagnosis would be missed clinically or radiographically, because pulmonary arterial pressure rises late in these diseases.

2. *Intracardiac or Intervascular Shunts.*—Edwards[5] has ably summarized the effects of intracardiac and intervascular shunts upon the pulmonary vasculature. Those that cause increased pulmonary blood flow (such as interatrial defect, anomalous pulmonary venous drainage) cause progressive intimal changes which eventually result in pulmonary hypertension. On the other hand, shunts which result predominantly in increased pulmonary arterial pressures (such as

high ventricular septal defect) will lead initially to increased musculature in the arteriolar walls ("fetalization of pulmonary vasculature"), although the chronically increased pulmonary pressures eventually will also produce intimal changes. It is conceivable that one cause of primary pulmonary hypertension is the abnormal persistence, after birth, of the fetal type of pulmonary vasculature. Persistence of fetal arteries has been described in two infants with idiopathic right ventricular hypertrophy.[9] Autopsy material may fail to throw light on such a possibility since at the time of death extensive sclerotic changes usually have taken place, whatever the cause of the hypertension.

Right heart catheterization and sampling of the chambers and brachial artery will detect the majority of such shunts. However, it is precisely when the pulmonary arterial pressure is high and the shunt is balanced that the diagnosis of primary pulmonary hypertension is most often suspected, and it is then that catheterization techniques by themselves are least effective. Shepherd and associates[2] have pointed out additional precautions that must be taken in such situations, particularly when the arterial saturation lies in the lower limits of normal. The cuvette oximeter is useful in localizing, during manipulation of the catheter, small left-to-right shunts that otherwise could be overlooked. Indicator dilution techniques will show up small right-to-left shunts which may be missed from the oxygen saturation of the blood; studies with radioactive potassium may be even more sensitive in doing this than the more widely used Evans blue. The presence of a balanced shunt in patent ductus arteriosus may be demonstrable only by simultaneous dye dilution curves determined in the femoral and brachial arteries. The magnitude of a left-to-right shunt can be increased upon breathing 100 per cent oxygen, and that of a right-to-left shunt may be increased upon breathing oxygen-poor mixtures. Simultaneous recording of pulmonary and systemic arterial pressures will tend to rule out a shunt if the relationship between the pressures in the two circuits changes on exercise or breathing different oxygen mixtures. Cyanosis is not uncommon in primary pulmonary hypertension because of the reduced cardiac output and consequently increased extraction of oxygen by the skin tissues ("peripheral cyanosis"). Moreover, peripheral arterial oxygen unsaturation is sometimes found at cardiac catheterization in the absence of a shunt. Barbiturate sedation and the position, discomfort, and anxiety concomitant with the procedure may contribute to hypoventilation. Repeat determination of the arterial saturation in the unmedicated patient will often show normal values in such a case. More complicated is the supervention of shunts in cases thought to represent primary pulmonary hypertension. Shepherd and associates[2] in their series list 4 such cases in whom a patent foramen ovale was thought to be a factor in right-to-left shunt secondary to primary pulmonary hypertension. In the absence of post-mortem confirmation it is difficult to establish such cases as representing primary pulmonary hypertension. Similarly, communications between pulmonary and bronchial arteries may become patent in pulmonary hypertension and lead to peripheral unsaturation when pulmonary pressures exceed systemic ones. Evans and associates[3] demonstrated such communications in post-mortem pulmonary arteriograms. They felt that these communications could not account for sig-

nificant shunting and that they were, therefore, the result rather than the cause of the pulmonary hypertension. However, it is conceivable that abnormal bronchial-pulmonic arterial communications give rise to considerable left-to-right flow and, eventually, hypertension. Such lesions would not be discoverable by catheterization and could be excluded only by indicator dilution curves.

A word may be said about the dangers of cardiac catheterization in primary pulmonary hypertension. Schafer and associates[10] have reported 3 deaths associated with this procedure in 3 cases of primary pulmonary hypertension; these were the only deaths in over 900 catheterizations. Other investigators[1-11] have reported deaths of patients with primary pulmonary hypertension after trivial surgical procedures. It has been suggested[11] that patients with this disease are particularly susceptible to barbiturates and that they do not tolerate the reduction of cardiac output caused by these drugs. The reduction in cardiac output has also been considered the basis of exertional syncope, which is sometimes seen in primary pulmonary hypertension. In our laboratory we have performed right heart catheterization in more than 12 cases, without any immediate mishap. Barbiturate premedication was used in most of these cases.

3. *Lesions of the Pulmonary Arterial Vasculature Other Than Those Due to Shunts.*—Under this heading, a large variety of lesions may be included; in fact, it is conceivable that if all the causes of such lesions were known, the diagnosis of primary pulmonary hypertension would no longer exist. The lesions may range from gross ones, such as agenesis of a pulmonary artery, chronic thrombosis of the major pulmonary artery,[12] multiple stenosis of pulmonary arteries,[13] and multiple pulmonary infarcts, to microscopic ones, such as schistosomiasis, amniotic fluid emboli, and microscopic thromboses. Some of the gross lesions can be ruled out with simple chest roentgenogram, but others may require demonstration by selective angiography or by injection of the pulmonary tree post mortem.[3] Although some of the microscopic lesions can be deduced from the clinical information concerning the case, many require microscopic demonstration. Even then, the etiology of the observed lesion may be moot. Thus, Shepherd and associates[2] state that 9 of their 10 cases occurred in women. It is true that 4 of these women had never been pregnant, and in 2 who were autopsied no evidence of amniotic emboli was found. But the question arises in these authors' series as to whether there was some connection between pregnancy or menstruation and the pulmonary lesions. Thromboses and lesions of the intima are even more difficult to interpret. Such obscure causes for multiple microthromboses as cryoglobulinemia[14] or sicklemia[15] may be overlooked. On the other hand, "bland" thromboses may be found in some lung sections in primary pulmonary hypertension which, when traced in serial sections, are associated with an intimal lesion in another section. Such thromboses have not been considered to be the cause of sufficient reduction of the vascular bed to account for the hypertension.[2] On the other hand, Evans and associates[3] describe foci of medial hypoplasia associated with intimal proliferations and thromboses, and they ascribe the primary hypertension to these.

4. *Obstruction of the Pulmonary Veins or of the Mitral Valve.*—Rheumatic mitral stenosis is the most common of this type of etiology, and in most cases

the left atrial enlargement demonstrated by the right anterior oblique esophagram is diagnostic. However, the left atrium is not always enlarged in mitral stenosis. Bentivoglio and associates[16] have described severe pulmonary hypertension in cases with "pure" mitral regurgitation. They feel that a left atrium which remains small, possibly because it has not been severely involved by the rheumatic process, will fail to act as a buffering reservoir and will transmit the increased pressure to the pulmonary vasculature. This is particularly likely to occur in congenital mitral stenosis or insufficiency, in which the left atrium is said to remain normal in size.[1] However, enlargement of the left atrium has been observed in cases of congenital mitral stenosis or regurgitation.[17,18] Normal or only slightly enlarged left atria with marked pulmonary hypertension have also been observed in rheumatic mitral stenosis (Case 3).

Theoretically, the presence of a normal "wedge pressure" associated with high pressure of the pulmonary artery is adequate evidence for ruling out mitral disease, as the former is thought to reflect left atrial pressures exclusively. However, in practice, this differentiation is far from accurate. Dickens and associates[19] have shown that significant mitral stenosis may exist in the presence of almost normal wedge pressure. A catheter thought to be "wedged" may not have been advanced sufficiently far (or cannot be advanced) and will record misleadingly high "wedge pressures." At other times, the tip of the catheter may be kinked or may touch the pulmonary arterial wall and indicate erroneously low "wedge pressures." Such errors are particularly likely to happen in patients with severe pulmonary hypertension, patients who may be seriously ill and have a markedly irritable myocardium which results in frequent ectopic beats during the procedure, so that a leisurely study is not feasible.

Left heart catheterization is, therefore, essential in making the diagnosis of primary pulmonary hypertension. Only in this manner can surgically remediable lesions of the mitral valve be ruled out. On the other hand, we have studied a case of presumably primary pulmonary hypertension in which the wedge pressure for some reason was high, but which has shown a normal left atrial pressure and no gradient across the mitral valve upon catheterization of the left heart. Admittedly, the risk of left heart catheterization is somewhat increased in patients as brittle as those with primary pulmonary hypertension. Nevertheless, the risk is justified inasmuch as it is the only means by which a correctable lesion of the mitral valve can be definitively ruled out.

The following case illustrates the fallacy of accepting the diagnosis of primary pulmonary hypertension in the absence of left heart catheterization. Moreover, it represents a very rare cause for pulmonary hypertension.

CASE REPORTS

CASE 1.—N. H., a 19-year-old white woman, was admitted on June 5, 1956, because of exertional dyspnea. She had been completely asymptomatic until 5 years prior to admission, when she had had "a bad cold" associated with cough and a slight amount of blood-tinged sputum. Her physician found a murmur and thought she had rheumatic fever; he prescribed rest for 6 months. She was subsequently seen by a competent cardiologist who made the diagnosis of mitral stenosis.

During these 6 months of rest, she tired easily, felt slightly dyspneic, and had a rapid pulse. She had no hemoptysis or fever except during the "cold"; nor was arthralgia or skin rash noted

at any time. Following this convalescence, she returned to school with moderate restriction of activities. She was not able to walk comfortably around one block. She had no pain in the chest, and no ankle edema, orthopnea, or paroxysmal nocturnal dyspnea. She had a severe cough with any cold, but not at other times.

Six months prior to admission, she started to note ankle edema, and became dyspneic at rest. Lying flat did not increase her dyspnea. She was digitalized and given mercurial diuretics, which resulted in a loss of weight of 17 pounds, and some improvement. She was catheterized at that time (see Table I).

TABLE I. CATHETERIZATION DATA (CASE 1)*

	OXYGEN CONTENT (VOL. %)	PRESSURE (MM. Hg)
Superior vena cava	12.4	
Inferior vena cava	11.3	
Right atrium	11.1, 11.4, 11.4	5
Right ventricle	11.2, 11.2, 11.1	118/2
Main pulmonary artery	11.1	118/60
Brachial artery	20.1 (87%)	130/100

Cardiac output = 4.7 L./min.

*These data were obtained through the courtesy of Dr. Asher Woldow, Albert Einstein Medical Center, Northern Division, Philadelphia, Pa.

For the last 6 months her general health was gradually declining. She could no longer tolerate the slight exertion required by her clerical job. She was dyspneic after walking 20 to 30 yards, but could still sleep flat. Her edema was fairly well controlled by Digoxin and one mercurial injection weekly. She noted cyanosis for the last 2 to 3 months; this occasionally appeared both in the hands and feet after exertion, but frequently also at rest, particularly in her toes when her legs were dangling.

On examination, the patient's healthy, attractive appearance contrasted with her severe illness. The pulse was 88; the blood pressure was 110/70 mm. Hg. Examination was entirely negative except for the heart. The lungs were clear to percussion and auscultation. The neck veins were not distended. MI was normal in intensity. The pulmonic second sound was accentuated, 2+, and the aortic second sound was normal. A blowing Grade 1 systolic murmur was heard at the apex, and a rough Grade 2 systolic murmur was heard along the left sternal border. No other murmurs were heard. No organs were palpable in the abdomen. Minimal pretibial edema was present. The feet were slightly cyanotic and became intensely cyanotic on dependency; no cyanosis was noted elsewhere.

Routine laboratory studies were normal. Hemoglobin was 14.4 Gm. Urinalysis was negative except for slight proteinuria. The ECG showed a normal sinus rhythm, peaked P waves, and right ventricular hypertrophy (Fig. 1). Roentgenograms of the heart (Fig. 2) showed 2+ generalized cardiac enlargement, 2+ right ventricle and pulmonary artery, enlargement of pulmonary vasculature, and normal left atrium. Maximum breathing capacity and spirogram were normal. Right heart catheterization was performed and the data are shown in Table I. Severe pulmonary hypertension was present. The pulmonary wedge pressure was not obtainable. There was no evidence for an intracardiac shunt.

A tentative diagnosis of primary pulmonary hypertension was made and the patient was discharged on digitalis and diuretic therapy. She was readmitted 3 months later because of persistent failure. Shortly after admission, pulmonary edema supervened and she died.

Necropsy data were made available through the courtesy of the Pathology Department of the Hahnemann Medical College and Hospital. The heart weighed 470 grams; its moderate enlargement was confined to the right ventricle. The myocardium of the latter was 1.2 cm. thick,

while that of the left ventricle measured 1.3 cm. The atrial walls appeared normal and were 3 mm. in thickness. No clot was found in the pulmonary artery. The endocardial surface of the left atrium was rough and showed patches of thickening; it was normal in the other chambers. The valves were grossly thin except for the mitral valve which was conically shaped without definition of commissures, its opening measuring 0.8 cm. in diameter. The mitral valve leaflets were thickened. Both coronary arteries arose from the left posterior sinus of Valsalva. Sections of the left atrium and ventricle revealed marked thickening of the endocardium due to fibroelastic proliferation; processes of this fribroelastic tissue radiated into the myocardium. The myocardium showed hypertrophied muscle fibers with bizarre type of nuclei and diffuse fibrosis. There were no Aschoff bodies or perivascular fibrosis. The mitral valves were thickened but not vascularized. The pulmonary arteries showed marked intimal proliferation. The final diagnosis was endocardial fibroelastosis involving the mitral valve.

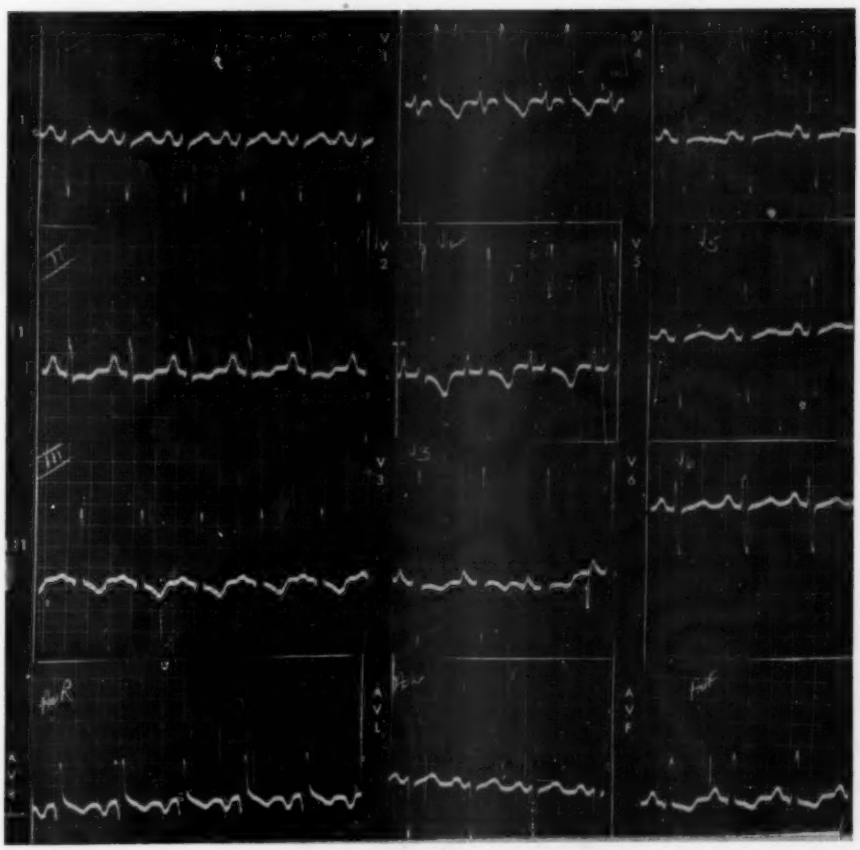

Fig. 1.—Case 1. ECG showing right ventricular hypertrophy and strain.

Comment.—The mitral diastolic rumble, which apparently had been heard previously, was no longer noted at the time of the first admission, probably because of decreased flow through the mitral valve. On the other hand, such a murmur has been observed in a case of primary pulmonary hypertension (Case 2), and in this latter case only left heart catheterization definitively ruled out mitral stenosis. The increasing intensity of the systolic murmur, heard only at the base on the first admission, but audible equally well at the apex during the second

admission, may represent increasing tricuspid regurgitation. Its mechanism is perhaps similar to that seen in severe mitral stenosis (Case 3), as described by Uricchio and associates.[20]

Chapman and associates[1] mention fibroelastosis as a cause of mitral valve obstruction in the absence of left atrial dilatation. However, they consider the disease to be confined to the pediatric group, and they state that electrocardiographic evidence of subendocardial injury and left ventricular hypertrophy are helpful clues. In this patient none of these factors were present. Moreover, in the case reported by Clark and associates[21] no ECG evidence of left subendocardial

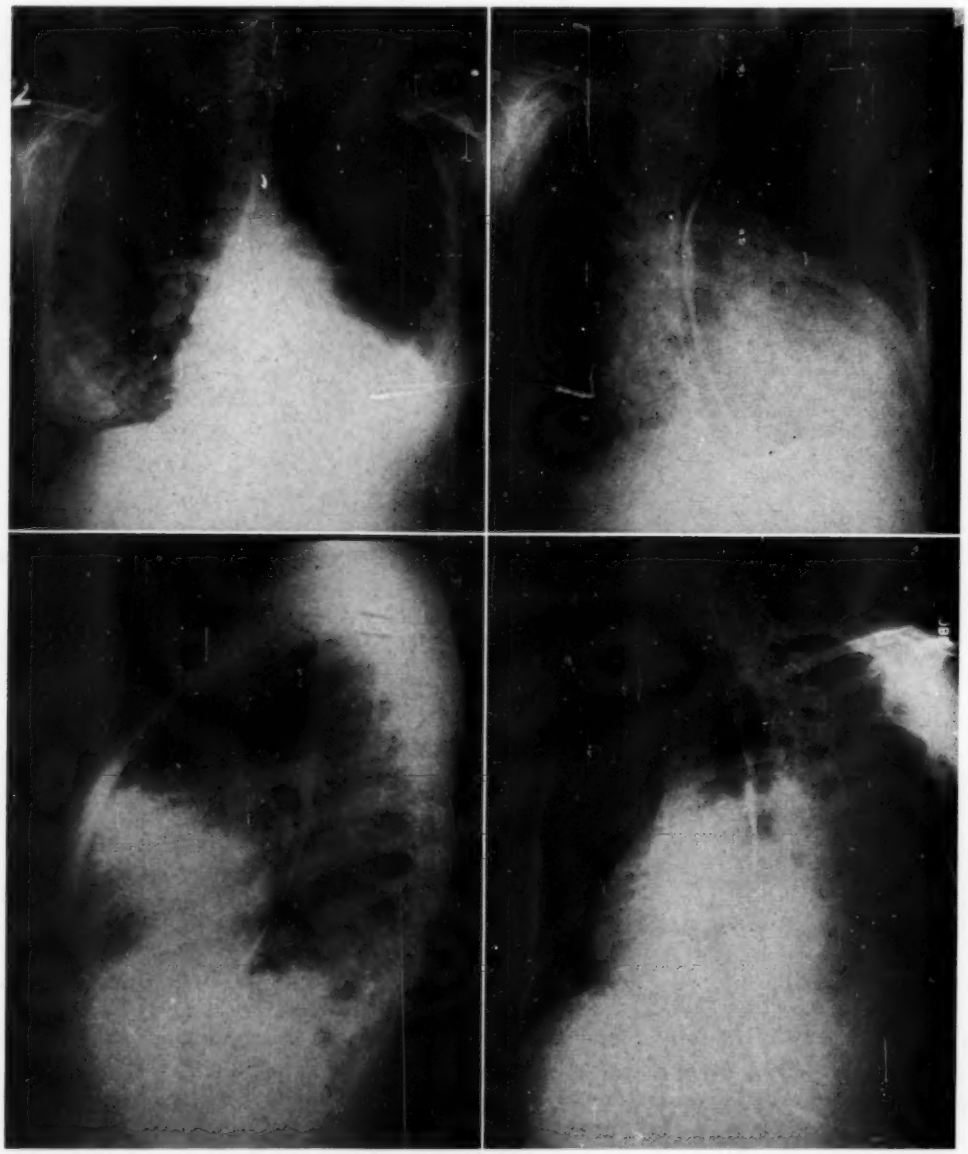

Fig. 2.—Case 1. Roentgenograms showing enlargement of the right ventricle, pulmonary artery, and left pleural effusion. The left atrium is normal.

injury was present; in fact, it was the absence of such evidence that was considered corroborative of Prinzmetal's view that the subendocardial region is silent. Incidentally, in Clark's case the presence of a "diastolic dip" in the right ventricular pressure tracing led to the erroneous diagnosis of constrictive pericarditis. This pressure contour was thought to be transmitted from the left side of the heart where both the left ventricle and the aortic valve were involved. A case with pulmonic insufficiency and idiopathic pulmonary hypertension in which the right ventricular pressure tracing was similar to that seen in constrictive pericarditis has been observed in this laboratory.[22]

Endocardial fibroelastosis is commonly associated with congenital cardiovascular malformations; the unusual origin of one of the coronary arteries in this case may be considered a benign malformation. The valves are affected in about half the cases.

By contrast, the following case, which represents primary pulmonary hypertension, was considered to be one of mitral stenosis (including the "typical" murmur) until absence of a gradient across the mitral valve was demonstrated by left heart catheterization.

CASE 2.—This 42-year-old white woman was well until 4 years prior to admission, when, during her third pregnancy, she developed chest pains. Following delivery she started noting exertional dyspnea and easy fatigability. Two-pillow orthopnea and peripheral edema appeared during the year of admission. She had episodes of syncope about once monthly. She never was cyanotic. A murmur was discovered 4 years prior to admission.

On physical examination she appeared misleadingly healthy. The pulse was 98; the blood pressure was 140/94 mm. Hg. Normal sinus rhythm was present. Significant findings were confined to the heart. MI was sharp. An opening snap, followed by a mid-late diastolic rumble, was best heard near the sternum. The pulmonic second sound was accentuated. An early blowing diastolic murmur was heard in the pulmonic area. No peripheral edema was present.

Routine laboratory studies were not remarkable. The electrocardiogram showed a normal sinus rhythm, peaked P waves, and right ventricular hypertrophy and strain. Roentgenograms showed an over-all increase of heart size (2+). The pulmonary artery was increased in diameter, the hilar vessels prominent, and the left atrium normal (Fig. 3).

Because of the auscultatory findings of mitral stenosis, enlarged pulmonary artery, and normal-sized left atrium, a presumptive diagnosis of Lutembacher's syndrome was made.

TABLE II. CATHETERIZATION DATA (CASE 2)

	OXYGEN CONTENT (VOL. %)	PRESSURE (MM. Hg)
Superior vena cava	13.6	—
Inferior vena cava	13.7	—
Right atrium	14.2, 15.1, 14.4	0
Right ventricle	13.7, 14.6	70/5
Pulmonary artery	14.2	70/32 (mean 45)
Left atrium	—	6
Left ventricle	—	90/4
Brachial artery	20.4 (94% saturated)	100/70 (mean 85)

Oxygen consumption	130 c.c./min.
Cardiac output	1.6 L./min.
Pulmonary vascular resistance	1,950 dynes-sec.-cm.$^{-5}$

Combined right and left heart catheterization was carried out. The data are listed in Table II. There was no evidence for an intracardiac shunt. No pressure gradient across the mitral valve was obtained. After the catheterization she developed hypotension with clinical findings suggesting cardiac tamponade. As pericardial taps were unproductive and her condition was deteriorating, a limited thoracotomy was carried out under Pentothal sodium anesthesia. Neither excess fluid or blood were found in the pericardial cavity. The patient was returned to her room in good condition, but shortly thereafter she again became markedly hypotensive. She died suddenly 4 days after the catheterization.

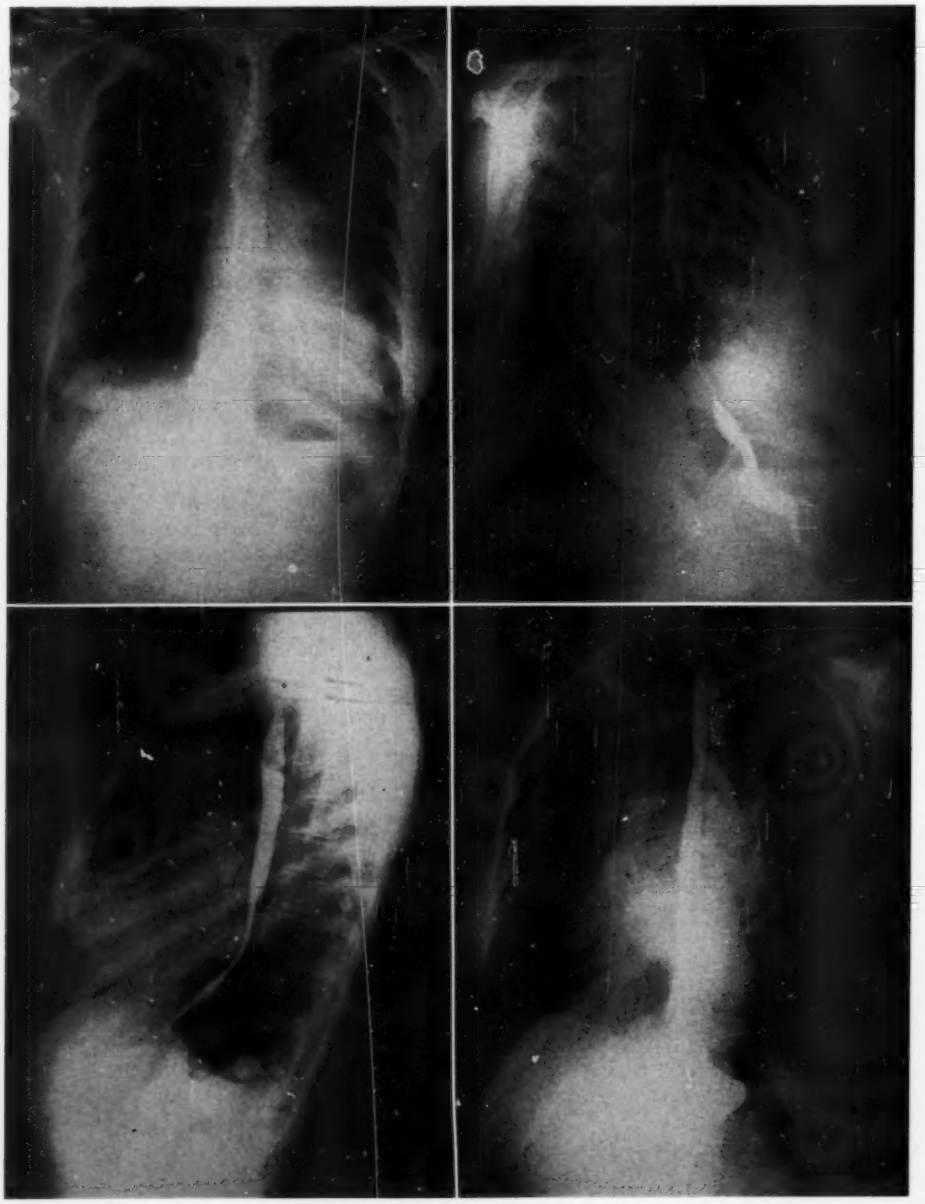

Fig. 3.—Case 2. Roentgenograms showing enlargement of the right ventricle, and pulmonary artery. The left atrium is normal.

Necropsy data were made available through the Pathology Department of Hahnemann Medical College and Hospital. There was marked hypertrophy of the right ventricle. The valves were normal and no intracardiac defect was present. The pulmonary artery showed marked dilatation and sclerosis. Microscopically, intimal thickening was seen in the pulmonary arterial tree, particularly in the smaller vessels, many of which had pin-point lumina.

Comment.—The diagnosis of primary pulmonary hypertension was definitely established by combined left and right heart catheterization. The genesis of the murmurs in this condition remains obscure. The mid-late diastolic murmur, interpreted as being due to mitral stenosis, was probably caused by a relative tricuspid stenosis. The systolic murmur in the pulmonic area or lower down along the sternum may have been due to a relative pulmonic stenosis, because of the dilated pulmonary artery as observed in atrial septal defects. Tricuspid regurgitation may also have accounted for the systolic murmur. This case confirms the previous observations that these patients are very fragile and may succumb to minor surgical procedures.

CASE 3.—E. P., a 43-year-old white woman, was admitted on Feb. 21, 1957, because of dyspnea on exertion. She had a vague history of joint pains at age 17. At 33, during her second pregnancy, a murmur was discovered. She was well until the age of 41 years, when fatigue, exertional dyspnea, and orthopnea began to appear and became progressive. Cyanosis was noted during the last 6 months.

On physical examination she appeared somewhat slender, slightly dyspneic, and orthopneic. Neck veins were slightly distended. Normal sinus rhythm was present. The apex beat was in the fifth intercostal space and anterior axillary line. MI was loud and split. The pulmonic second sound was markedly accentuated. A Grade 3 systolic murmur was audible at the apex, and a Grade 2 blowing systolic murmur at the pulmonic area; no diastolic murmurs were heard. The finger tips were slightly clubbed and cyanotic.

The ECG showed tall P waves in the limb leads, normal sinus rhythm, and right ventricular hypertrophy. Roentgenograms showed 2+ generalized cardiac enlargement; right ventricle, 1 to 2+; left atrium, 1+; and left ventricle, 2+; the pulmonary arteries were increased 2+ (Fig. 4).

Right heart catheterization was performed first because congenital heart disease was suspected. The data obtained are listed in Table III. Because of the inconclusive results, left heart

TABLE III. CATHETERIZATION DATA (CASE 3)

	OXYGEN CONTENT (VOL. %)	PRESSURE (MM. Hg)
Inferior vena cava	9.6	—
Right atrium	10.0; 10.1	(0)
Right ventricle	9.6; 10.8	95/0
Main pulmonary artery	10.5	92/44 (mean 68)
Brachial artery	17.5 (83% saturated)	110/68
Left atrium	—	40
Left ventricle	—	142/3
Brachial artery	—	149/99
Left atrial-left ventricular filling pressure gradient	—	38

Oxygen consumption	137 c.c./min.
Cardiac output	2.0 L./min.
Pulmonary vascular resistance	1,120 dynes-sec.-cm.$^{-5}$

catheterization was carried out the next day. This study revealed an elevated left atrial pressure and a marked pressure gradient between the left atrium and left ventricle during ventricular filling, consistent with mitral stenosis. A right ventriculogram (Fig. 5), performed by the transthoracic injection of Hypaque into the right ventricle,[24] showed 3+ tricuspid insufficiency.

The patient underwent right-sided thoracotomy,[25] with the diagnosis of mitral stenosis and tricuspid insufficiency. The mitral valve was found to be heavily calcified, immobile, admitting only a finger tip, and showing marked anterior and posterior fusion with minimal mitral regurgitation. The valve was opened to 2½ fingerbreadths and the subvalvular fusion was split. The tricuspid valve was then explored and found to be organically normal. Regurgitation was demonstrable. The atrial septum was intact.

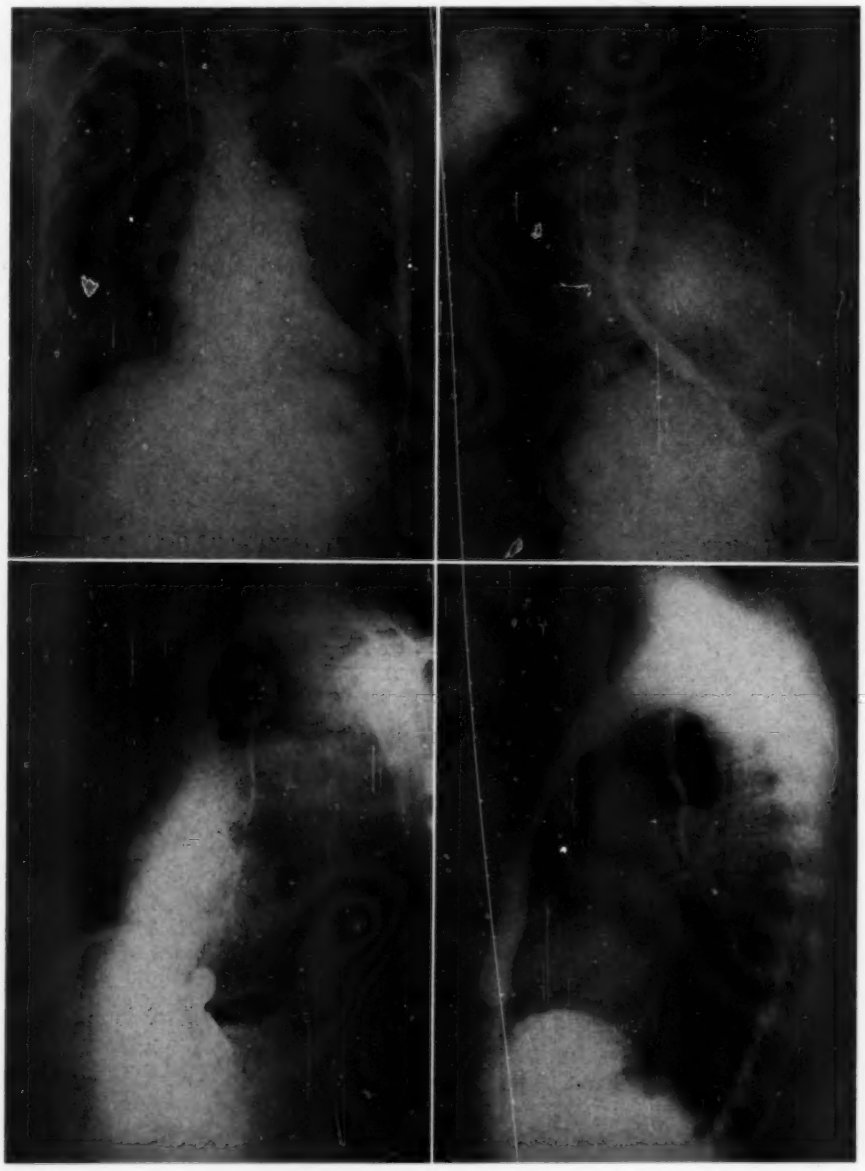

Fig. 4.—Case 3. Roentgenograms showing enlargement of the right ventricle, pulmonary artery, and left atrium.

Comment.—This case has many features of interest in the study of pulmonary hypertension. Although in retrospect the diagnosis of mitral stenosis could have been made on the roentgenograms, this diagnosis was not at all obvious to clinicians who have had extensive experience with this lesion. However, it can readily be seen that some increase in generalized cardiac enlargement might have completely masked the slight degree of left atrial enlargement. The presence of peripheral arterial unsaturation was very misleading, and remains unexplained. Hypoventilation during catheterization, and inadequate gas diffusion across the alveolar membrane because of pulmonary congestion, may have played a part. A right-to-left shunt through opened pulmonary-brachial anastomoses is unlikely as long as the pulmonic pressure was below the systemic.

This case fits in well with Uricchio and associates' series,[20] in which a loud apical systolic murmur was heard in cases of mitral stenosis without mitral regurgitation. In such cases the results of the right ventriculogram throw light on one possible genesis of the systolic murmur in primary pulmonary hypertension, and also illustrate the importance of detecting patients with tight mitral

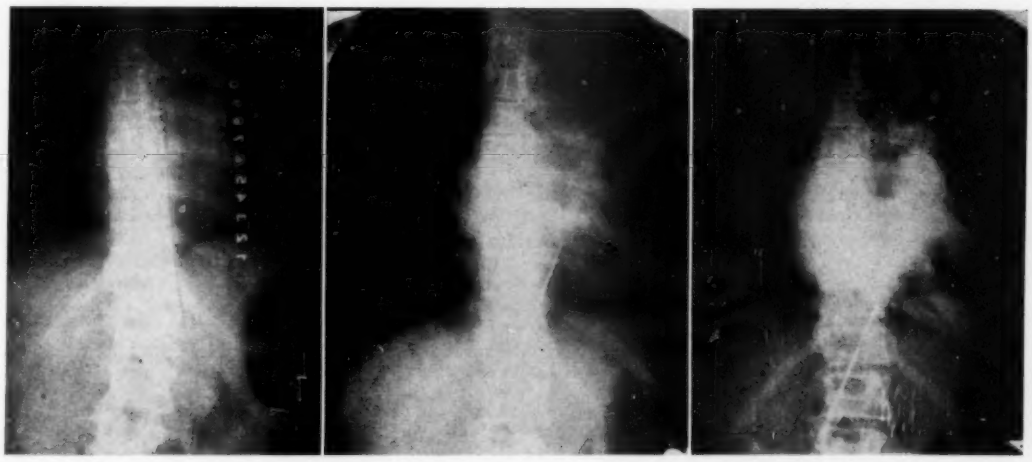

Fig. 5.—Roentgenograms showing right ventriculogram. Hypaque has been injected into the right ventricle. Note immediate opacification of the enlarged right atrium.

stenosis who may be denied a lifesaving commissurotomy because mitral regurgitation is considered the major lesion. These authors have stressed the point that no specific clinical features (except possibly pulsation of the neck veins) distinguish tricuspid from mitral regurgitation. Even the pressure tracing obtained in the right atrium in this case was not characteristic of regurgitation, and the right atrial pressure was normal. Left ventriculography is of great aid in demonstrating the absence of significant mitral regurgitation in such cases. Right ventriculography, although of great academic interest in demonstrating the genesis of the murmur in such cases, is of little practical value because the tricuspid regurgitation tends to subside as soon as the mitral obstruction is relieved.

SUMMARY

The difficulties in diagnosing primary pulmonary hypertension are discussed and the criteria to be fulfilled are listed. The importance of left heart catheterization in excluding cases of "occult mitral stenosis," a remediable form of heart disease, is stressed. A case is described in which such disease was present with the unusual etiology of endocardial fibroelastosis involving the mitral valve.

REFERENCES

1. Chapman, D. W., Abott, J. P., and Latson, J.: Circulation **15**:35, 1957.
2. Shepherd, J. T., Edwards, J. E., Burchell, H. B., Swan, H.J.C., and Wood, E. H.: Brit. Heart J. **19**:70, 1957.
3. Evans, W., Short, D. S., and Bedford, D. E.: Brit. Heart J. **19**:93, 1957.
4. Dresdale, D. T., Michton, R. J., and Schultz, M.: Bull. New York Acad. Med. **30**:195, 1954.
5. Edwards, J.: Circulation **15**:164, 1957.
6. Brenner, O.: Arch. Int. Med. **56**:976, 1935 and **56**:1189, 1935.
7. De Navasquez, S., Forbes, J. R., and Holling, H. E.: Brit. Heart J. **2**:177, 1940.
8. Dresdale, D. T., Schultz, M., and Michton, R. J.: Am. J. Med. **11**:686, 1951.
9. Wolman, M.: Am. J. M. Sc. **220**:133, 1950.
10. Schafer, H., Blain, J. M., Ceballos, R., and Bing, R. J.: Ann. Int. Med. **44**:505, 1956.
11. Inkely, S. R., Gillespie, L., and Funkhauser, R. K.: Ann. Int. Med. **43**:396, 1955.
12. Hollister, L. E., and Cull, V. L.: Am. J. Med. **21**:312, 1957.
13. Arvidson, H., Karnell, J., and Moller, T.: Acta radiol. **44**:209, 1955.
14. Muirhead, E. E., Montgomery, P. O., and Gordon, C. E.: A.M.A. Arch. Int. Med. **89**:41, 1952.
15. Moser, K. M., and Shea, J. G.: Am. J. Med. **22**:561, 1957.
16. Bentivoglio, L., Uricchio, J., and Likoff, W.: Am. J. Med. **24**:193, 1958.
17. Downing, D. F.: Personal communication.
18. Brando, J. L., Javett, S. N., Adler, D. I., and Kessell, I.: Circulation **15**:358, 1957.
19. Dickens, J., Raber, G., Woldow, A., Larange, G., and Goldberg, H.: New England J. Med. **256**:1017, 1957.
20. Uricchio, J., Bentivoglio, L., Gilman, R., and Likoff, W.: Am. J. Med. Tricuspid Regurgitation Masquerading as Mitral Regurgitation in Patients With Pure Mitral Stenosis. (In press.)
21. Clark, G. M., Valentine, D., and Blount, S. G.: New England J. Med.: **254**:349, 1956.
22. Dickens, J., Raber, G., and Goldberg, H.: Ann. Int. Med. Dynamic Pulmonary Regurgitation Associated With a Bicuspid Valve. (In press.)
23. Musser, B., and Goldberg, H.: J. Thoracic Surg. **34**:414, 1957.
24. Lehman, J. S., Musser, B. G., and Lyheus, H. D.: Am. J. Rad., Rad. Ther. and Nucl. Med. **87**:207, 1957.
25. Bailey, C. P., and Morse, D.: J. Thoracic Surg. **33**:427, 1957.

Clinical Value of Simultaneous-Lead Electrocardiograms

Thomas N. James, M.D., and Raymond W. Bryant, M.D., New Orleans, La.*

In 1912, Sir Thomas Lewis[1] suggested that little remained to be discovered in the field of electrocardiography. The basic work of Wilson[2] and Sodi-Pallares,[3] and the clinical investigations of Myers[4] are notable examples of the prematurity of this prophecy. Not only are new advances continuing to be made, but some of the older techniques have not been fully exploited.

One example of such a technique is simultaneous-lead electrocardiography. Although multiple-lead electrocardiograms are commonly published in European literature, single-lead electrocardiograms are most usually employed in clinical practice in the United States. In most large medical centers multiple-channel machines are currently being employed, but usually they are used to record simultaneous pressure tracings or phonocardiograms with one electrocardiographic lead, rather than two or more leads.

Some of the advantages of simultaneous electrocardiographic leads are readily apparent. In order to explore as many such advantages as possible, and thereby assess a fuller potential of the technique, this study was undertaken.

MATERIAL AND METHODS

During a period of 1 year, multiple-lead electrocardiograms were made on hospitalized patients having abnormal standard electrocardiograms. The former tracings were then studied to determine whether they were superior to the latter tracings.

A two-channel, direct-writer electrocardiograph was employed for most of the electrocardiograms; a photographic ("twin-beam") model was used in some cases. Paper speed was 50 mm. per second. For endocardial tracings obtained during cardiac catheterization and for the use of an exploring monitor electrode, as in pericardial paracentesis, the exploring electrode was set on the V lead position.

RESULTS

The simultaneous recording of two different electrocardiographic leads facilitates the precise definition of all complexes. Such description was of clinical importance in the following circumstances.

From the Section on Cardiology, Ochsner Clinic, New Orleans, La.

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*Fellow in Internal Medicine, Alton Ochsner Medical Foundation. Present address: La Jolla, Calif.

Arrhythmias.—In the specific diagnosis of tachycardia, establishment of the presence or absence of P waves, and their relationship to QRS, is of cardinal importance. For example, differentiation between supraventricular tachycardia with bundle branch block and ventricular tachycardia depends upon this particular point. The presence of P waves in some serially obtained leads and not in others can be of only presumptive reliability, for the pacemaker may change in the interim. By the simultaneous recording of one lead with clear P waves and of another without them, the location of the atrial complex in the latter lead can be determined (Fig. 1).

By the simultaneous recording of two leads from opposite surfaces of the heart (e.g., V_1 with V_6), the location of a ventricular ectopic pacemaker can be reasonably defined. Of even more importance, one can decide whether there is more than one ectopic ventricular focus (Fig. 2).

Electrolyte Disturbances.—Separation of the T and U waves has become of greater importance since recognition that potassium and calcium disturbances are reflected in the repolarization complexes. Such separation is at times quite difficult if the cardiac rate is rapid, since the T, U, and P complexes tend to obscure each other. By selecting a lead with a distinct P wave, and recording this lead with one having clear T and U waves, one may determine the respective locations of all three complexes (Fig. 3).

Intrinsicoid Deflections.—It is well known that the initial portion of a QRS complex may be isoelectric. Since an important basis for the diagnosis of ventricular hypertrophy is a delay in the time of the intrinsicoid deflection, the exact measurement of this time depends on establishment of the exact onset of the complex. By the simultaneous recording of Leads V_1 and V_6, which subtend the epicardium of the right and left ventricles, respectively, the earliest onset of electrical activity in either may be taken as the same for both. This is often of value in identifying the isoelectric portion of the Q wave in V_6, and thereby enables accurate QRS measurement in that lead (Fig. 4).

In addition to ventricular hypertrophy, exact definition of Q in V_6 is of importance in the diagnosis of bundle branch block, since Rodriguez and Sodi-Pallares[5] demonstrated that the direction of septal and free ventricular wall vectors is at least as important as the total duration of QRS.

Recently, Ziegler[6] demonstrated with clinicopathologic and cardiac catheterization data that the same principle may be applied in the differential diagnosis of right and left atrial enlargement. He noted that in right atrial enlargement the P wave in V_1 had an initial maximal positivity, since the electrically predominant right atrium was underlying that electrode and the vector of atrial activation was initially and predominantly toward V_1. Conversely, with left atrial enlargement the major atrial vector was away from Lead V_1, and the initial positivity of P in that lead was then brief and followed by a late maximal negativity. In leads from the left precordium (V_6) the opposite occurred, namely, with left atrial enlargement there was late maximal positivity and with right atrial enlargement there was late isoelectric or negative P wave (Fig. 5).

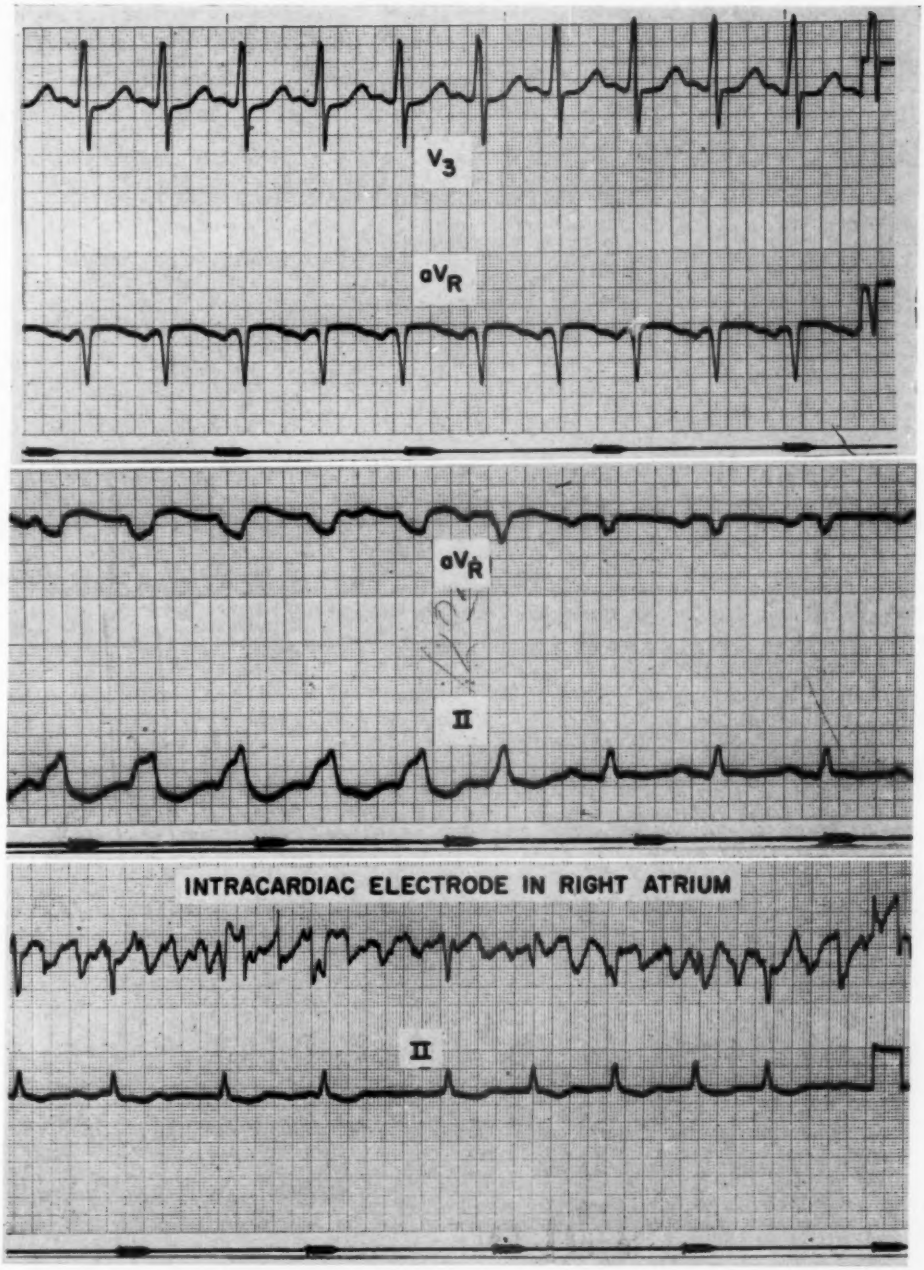

Fig. 1.—*A*, This patient had sinus tachycardia (144 per min.). The P wave was best seen in aV_R, the T wave in V_3. *B*, This patient had ventricular tachycardia which converted to sinus rhythm after he received 1.4 Gm. of intravenous quinidine. Note the P waves followed by aberrant QRS in both leads just prior to conversion. *C*, This patient had mitral stenosis and atrial fibrillation. Location of QRS in Lead II permits identification of QRS from the lead inside the fibrillating right atrium.

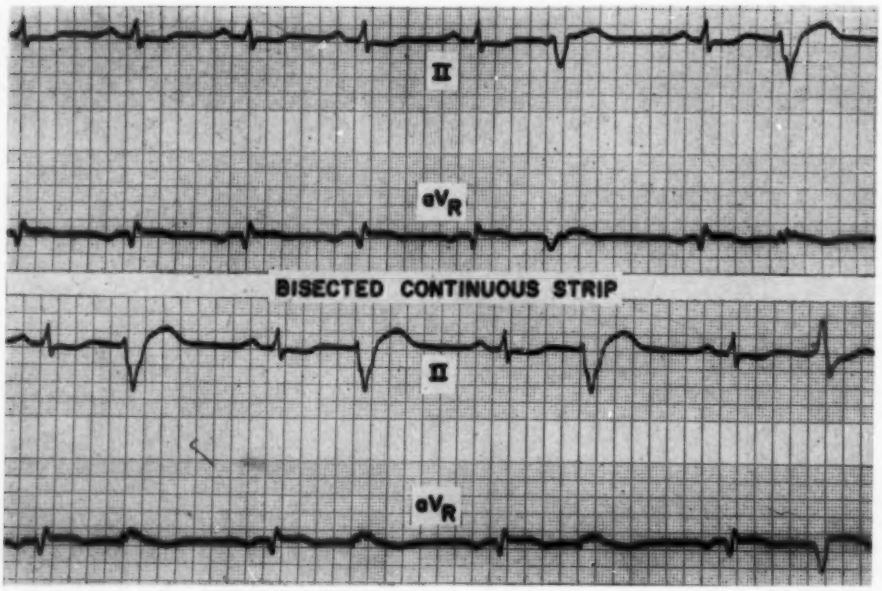

Fig. 2.—This patient had paroxysmal bigeminal rhythm due to atherosclerotic heart disease. There were three varieties of ventricular premature beats (or varying spread of excitation from a single focus). The sustained bigeminal beats were always different from the initial one at the onset of the paroxysm and the last one before the paroxysm ended.

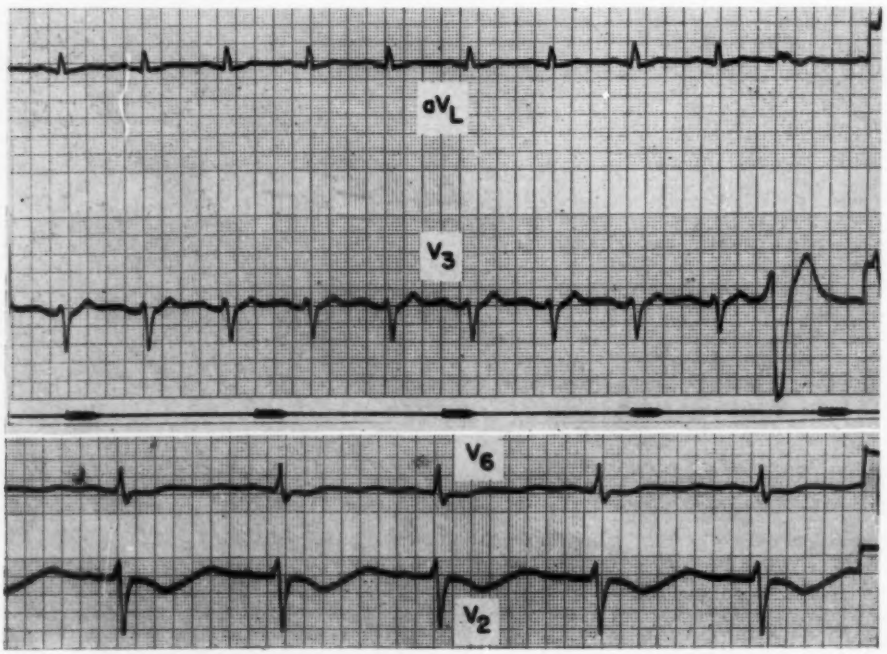

Fig. 3.—*A*, This patient had hypercalcemia due to widely metastatic mammary carcinoma. Note the short Q-T interval. The P wave was best shown in aV_L, the T in V_3. Serum calcium was 6.4 mEq. *B*, This patient had hypokalemia and an adrenal cortical adenoma. Serum potassium was 2.7 mEq. The U wave was best seen in V_2.

Monitoring Leads.—Use of an endocardial electrode during cardiac catheterization is of assistance in determining the location of the tip of the catheter, which location sometimes cannot be definitely established by fluoroscopy and manometry (Fig. 6). It is also helpful in recognizing when the tip of the catheter is pressing against the endocardium, because of the inscription of an injury potential at those times; such a situation is conducive to development of arrhythmias, in our experience. By the simultaneous recording of an extracardiac lead, the identification of all components of the endocardially recorded complexes, some of which assume bizarre appearances, is considerably simplified.

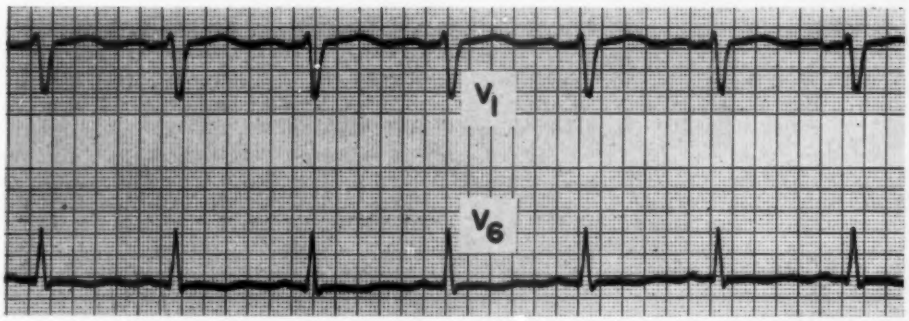

Fig. 4.—This patient had left ventricular hypertrophy due to hypertension from chronic glomerulonephritis. The heart weighed 550 grams at necropsy. Note the isoelectric portion of Q in V_6 and earlier onset of R in V_1.

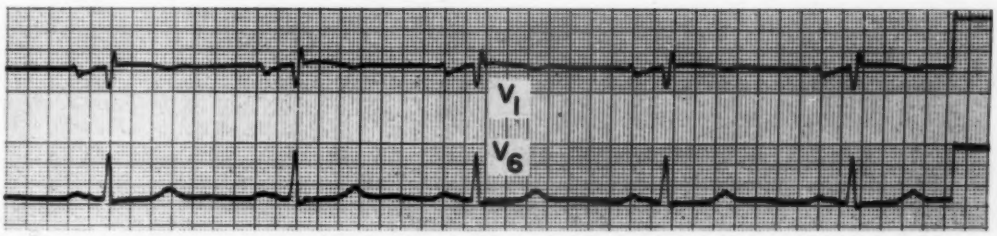

Fig. 5.—This patient had mitral stenosis due to rheumatic heart disease. See text for description of P-wave changes.

It has been reported recently that an electrode attached to the exploring needle during pericardial paracentesis allows the operator to know the exact location of the tip of the needle in relation to the ventricular epicardium.[7] This has been true in our experience; the complexes recorded from the exploring needle immediately increase in amplitude and pronounced S-T elevation occurs when the epicardium is touched. Others have found simultaneous-lead electrocardiography useful for orientation in esophageal electrocardiography for the differential diagnosis of arrhythmias.[8]

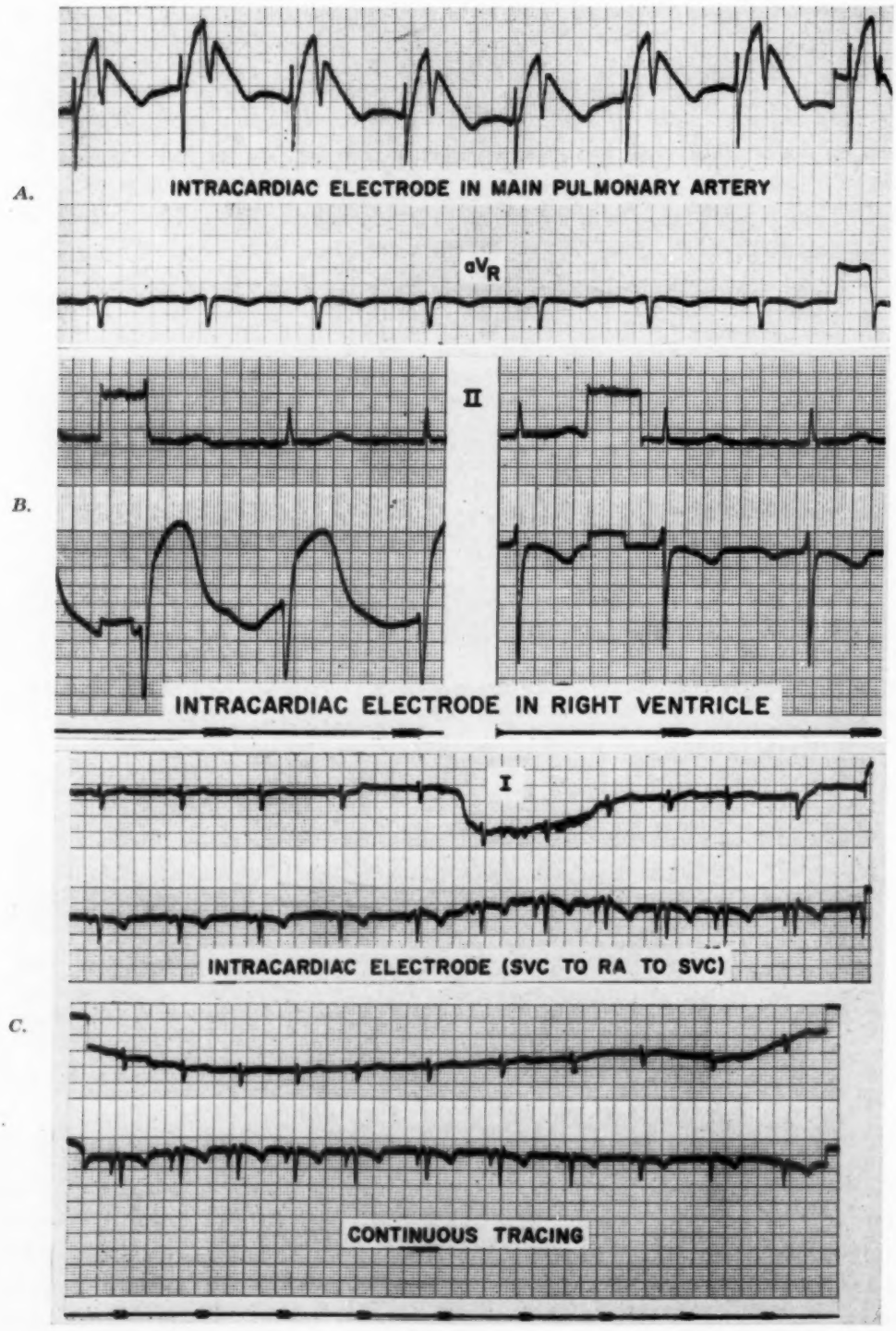

Fig. 6.—*A*, This patient had interventricular septal defect, illustrating the orienting value of a simultaneously recorded extracardiac lead. *B*, This patient had Rendu-Osler-Weber disease. Note elevation of S-T when the catheter is touching the endocardium (left) and the isoelectric S-T when it is not (right). *C*, This patient had Eisenmenger's complex. The tip of the catheter passes from the superior vena cava to the right atrium and back to the superior vena cava. Change in the contour of the P wave allows localization of the tip of the catheter.

DISCUSSION

In the haste and fascination of developing new diagnostic instruments we sometimes overlook some of the potentialities of older methods. The foregoing brief review suggests a few of the advantages of simultaneously recording different electrocardiographic leads. There are undoubtedly others.

Generally, these advantages are expressed in a better definition of P, QRS, T, and U by simultaneously recording leads that show one or more of these complexes most clearly with other leads that do not. For the meticulous electrocardiographer this precise definition is indispensable.

With direct or semidirect leads, such as those obtained from the esophagus or via a catheter from inside the heart, the simultaneous inscription of a familiar standard lead is of obvious orienting value.

From the standpoint of office efficiency, two additional advantages of simultaneous-lead electrocardiograms may be mentioned. First, recording of two leads at a time reduces (but of course does not halve) the time necessary to complete an electrocardiogram. Second, certain electrocardiographs, which record from two galvanometers on paper of ordinary width, permit considerable saving in the amount of paper used.

SUMMARY

Among the advantages of simultaneously recorded electrocardiographic leads, the following may be listed: (1) identification of the pacemaking focus in arrhythmias and premature beats; (2) separation of the T, U, and P waves in electrolyte disturbances; (3) timing of the onset of the intrinsicoid deflection of QRS and P waves; (4) monitoring of certain exploring leads, as in endocardial electrocardiography during cardiac catheterization, with a more familiar standard lead.

REFERENCES

1. Lewis, T.: Cited by Kossmann, C. E.: Am. J. Med. **14**:389, 1953.
2. Wilson, F. N.: Selected Papers, edited by F. D. Johnston and E. Lepeschkin, Ann Arbor, 1954, Edwards Bros., Inc.
3. Sodi-Pallares, D.: New Bases of Electrocardiography, St. Louis, 1956, The C. V. Mosby Company.
4. Myers, G. B.: The Interpretation of the Unipolar Electrocardiogram, St. Louis, 1956, The C. V. Mosby Company.
5. Rodriguez, M. I., and Sodi-Pallares, D.: AM. HEART J. **44**:715, 1952.
6. Ziegler, R. F.: Electrocardiography in Infants and Children, Lectures to the Mississippi Heart Association, Jackson, Miss., April 1-2, 1957.
7. Bishop, L. H., Jr., Estes, E. H., Jr., and McIntosh, H. D.: J.A.M.A. **162**:264, 1956.
8. Kistin, A. D., and Bruce, J. C.: AM. HEART J. **53**:65, 1957.

Direct Left Ventricular Puncture in the Evaluation of Aortic and Mitral Stenosis

Paul N. Yu, M.D., Frank W. Lovejoy, Jr., M.D.,* Bernard F. Schreiner, M.D.,** Robert H. Leahy, M.D.,**** C. Alpheus Stanfield, M.D.,*** and Heinz Walther, M.D.,**** Rochester, N. Y.*

In patients with aortic and/or mitral stenosis, simultaneous measurement of blood flow and pressure gradients across the respective valves provides precise information regarding the severity of obstruction at either valve and the presence of left ventricular failure. This requires the determination of cardiac output and the recording of left atrial, left ventricular, and aortic pressures either simultaneously or in rapid succession. Mean left atrial pressure may be estimated indirectly from the pulmonary artery wedge or pulmonary "capillary" pressure.[1,2] Central aortic pressure may be approximated by brachial or femoral artery pressure, particularly in patients with aortic stenosis.[3,4] Left ventricular pressure may be recorded by left heart catheterization through the posterior chest wall[5,6] or through a bronchoscope.[7]

Direct left ventricular puncture has been used in selective angiocardiography[8,9] and in studies of left ventricular pressure-volume relationship.[10] Recently, Brock, Milstein and Ross[11] described a method of percutaneous left ventricular puncture in the assessment of aortic stenosis. Physiologic data from 28 cases of aortic stenosis studied by these investigators were published.[12] The method is now under study in several medical centers.[13-15]

This paper presents data obtained with this technique combined with right heart catheterization in patients with aortic and/or mitral stenosis.

From the Chest Laboratory of the Department of Medicine, the University of Rochester School of Medicine and Dentistry, and the Medical Clinics of Strong Memorial and Rochester Municipal Hospitals, Rochester, N. Y.

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*Assistant Professor of Medicine, University of Rochester School of Medicine and Dentistry.

**Instructor in Medicine, University of Rochester School of Medicine and Dentistry; Postdoctorate Fellow in Cardiology, National Heart Institute.

***Instructor in Medicine, University of Rochester School of Medicine and Dentistry; American Trudeau Society Fellow.

****Research Fellow in Medicine, University of Rochester School of Medicine and Dentistry.

TABLE I. HEART RATE, BLOOD PRESSURE, AND ARTERIOVENOUS OXYGEN DIFFERENCE BEFORE AND DURING LEFT VENTRICULAR PUNCTURE

PATIENTS	DURING CARDIAC OUTPUT DETERMINATION					DURING LEFT VENTRICULAR PUNCTURE					
	H.R.	BA	$C_{a_{O_2}}$	$C_{V_{O_2}}$	A-V O_2 DIFF.	H.R.	BA	$C_{LV_{O_2}}$	$C_{a_{O_2}}$	$C_{V_{O_2}}$	A-V O_2 DIFF.
W.N.	100	—	14.60	9.53	50.7	100	104/51	—	—	—	—
C.M.	105	140/63	20.00	11.91	80.9	116	140/60	—	—	—	—
H.G.	95	126/52	17.72	7.90	98.2	88	135/57	17.38	17.55	8.36	95.2
A.B.	115	—	17.87	12.45	54.2	108	—	—	—	—	—
R.L.	82	139/59	19.80	15.80	40.0	83	147/61	—	—	—	—
M.D.	59	145/81	16.92	11.62	53.0	76	147/83	17.54	17.01	11.18	58.3
C.L.	80	185/84	17.13	14.20	29.3	86	221/71	—	—	—	—
E.K.	73	112/71	20.75	15.84	49.1	72	122/61	—	—	—	—
C.N.	67	121/47	17.41	10.49	69.2	77	105/47	16.94	17.17	10.54	66.3
P.S.	70	110/83	19.31	14.22	50.9	68	110/64	—	19.78	14.24	55.4
H.McD.	110	145/76	18.33	14.20	41.3	116	155/75	18.40	18.20	13.73	44.7
M.Sn.	83	125/64	18.01	10.58	74.3	85	118/59	18.13	18.02	10.07	79.5
V.H.	126	124/77	18.37	15.57	28.0	112	138/89	18.80	—	—	—
B.M.	93	160/94	18.05	13.02	50.3	105	156/104	—	18.47	12.51	59.6
F.R.	72	94/50	20.83	16.84	39.9	75	94/53	—	20.57	16.86	37.1
R.F.	80	121/68	19.28	14.51	47.7	80	116/70	—	18.96	13.27	56.9
M.S.	95	110/84	20.16	14.89	52.7	98	112/78	21.09	21.12	14.94	61.8
C.McL.	70	120/65	19.16	15.06	41.0	85	123/79	19.62	19.26	15.29	39.7
R.S.	80	147/63	18.40	14.71	36.9	79	149/60	17.54	18.63	—	—
E.S.	84	180/60	20.76	15.69	50.7	80	175/60	—	21.59	15.37	52.2
A.H.	66	110/55	17.87	14.00	38.7	65	105/52	17.52	18.02	13.72	43.0
F.Z.	80	122/76	19.30	14.34	49.6	80	126/74	18.92	—	13.85	50.7
H.Ri.	95	133/70	17.93	11.45	64.8	100	123/75	—	—	—	—
G.G.	62	174/48	14.47	7.90	65.7	66	174/44	14.06	14.43	7.16	72.7
H.R.	92	111/66	17.06	12.85	42.1	104	112/69	17.53	—	13.11	44.2
M.P.	85	154/76	15.05	9.88	51.7	75	142/78	15.03	—	9.68	53.5
R.W.	72	115/61	17.60	13.46	41.4	72	112/54	—	—	—	—
K.M.	65	134/67	20.68	16.16	45.2	70	137/72	20.95	20.87	16.92	40.3
J.W.	58	144/72	16.05	9.48	75.7	50	179/82	—	15.85	8.33	75.2
J.Wa.	66	100/75	19.53	16.40	31.3	60	108/78	—	—	—	—

H.R. = heart rate (beats/min.).
B.A. = brachial or femoral artery systolic and diastolic pressures (mm. Hg).
$C_{a_{O_2}}$ = oxygen content of arterial blood (vol. %).
$C_{V_{O_2}}$ = oxygen content of mixed venous blood (vol. %).
$C_{LV_{O_2}}$ = oxygen content of left ventricular blood (vol. %).
A-V O_2 diff. = arteriovenous oxygen difference (c.c./L.).

TABLE II. HEMODYNAMIC DATA FROM EIGHT PATIENTS WITH AORTIC AND/OR MITRAL STENOSIS

PATIENT	AGE, SEX, BSA RHYTHM	DIAGNOSIS	PERIODS OF STUDY	BLOOD FLOW					R.Q.	Sa_{O_2} (%)	PRESSURES (MM. Hg)												RESISTANCES (DYNES-SEC./CM.^{5})				STROKE WORK AGAINST PRESSURE (GM.M./M.^{2}/BEAT)			VALVE AREA (CM.^{2})	
				$\dot{V}_{O_2}$	A-vO_2 DIFF.	C.I.	H.R.	S.I.			RA (M)	RV (S/D)	PA		"PC" (M)	LV		BA			FA			TSR	TPR	PVR	"LHR"	RV	LV	TOTAL EFFECTIVE	MVA	AVA
													S/D	M		S/D	SM	S/D	M	SM	S/D	M	SM									
R.S.	38 M 1.82 S.R.	Aortic stenosis	R	150	36.9	4.1	80	51	0.77	97.0	2	30/4	30/14	20	12	193/10	147		—		147/63	83	89	880	210	60	150	13	99	52	—	0.8
W.N.	47 M 1.70 S.R.	Aortic stenosis	R	145	50.7	2.9	98	29	—	91.4	6	59/7	75/36	55	30	180/28	136		—		104/51	72	74	1,200	890	400	490	20	36	18	—	0.4
A.B.	44 M 1.93 A.F.	Mitral stenosis and aortic stenosis	R	165	54.2	3.1	52	60	0.86	99.1	4	38/4	35/14	20	11	171/7	117		—		149/64	96	100	1,270	260	120	140	14	93	76	2.1	1.0
H.McD.	47 F 1.36 S.R.	Mitral stenosis and aortic stenosis	R	158	41.3	3.8	108	35	0.85	92.7	2	49/3	49/16	27	—	—			—		145/76	92	—	1,410	410	—	—	12	—	—	—	—
			E	248	—	—	126	—	—	—	—	—	64/23	39	31	—			—			—	—	—	—	—	—	—	—	—	—	—
			R	144	44.7	3.3	114	29	—	92.1	—	—	52/26	32	25	202/5	152		—		155/75	99	101	1,700	560	120	440	—	60	39	1.5	0.5

B.M.	44 F 1.54 A.F.	Mitral stenosis	R E	150 190	50.3 65.9	3.0 2.9	86 109	35 23	0.81 0.93	96.6 94.8	1 —	46/4 86/0	51/24 88/40	30 51	20 32	166/8 —	— —		— —		166/104	120 —	—	2,040 —	520 1,240	170 460	350 780	14 21	53 —	53 —	1.0 —	—
P.S.	40 M 1.62 A.F.	Mitral stenosis	R E	133 272	50.9 93.9	2.6 2.9	72 88	36 33	0.86 0.79	98.6 98.0	7 —	44/5 —	39/19 61/33	30 42	25 31	130/1 —	—		— —		126/78	94 —	—	1,730 1,500	570 720	100 190	470 530	8 16	46 40	46 40	0.8 —	—
M.D.	41 F 1.76 A.F.	Mitral stenosis with myocardial insufficiency	8/13/57 R E 9/13/57 R	115 354 103	58.2 118.9 53.0	2.0 3.0 1.9	60 180 65	36 16 30	0.83 0.93 0.85	96.0 98.6 96.9	10 — 12	48/12 63/15 52/13	48/21 82/51 52/28	31 65 37	21 48 21	— — 130/16	— —	118/70 147/83	88 — 105	— — —	153/81	— — 104	— — —	1,960 — 2,390	640 980 820	210 260 360	430 720 460	10 — 10	— — 37	— — 37	1.1 — 1.2	— — —
E.K.	30 M 1.93 S.R.	Mitral stenosis with myocardial insufficiency	R E	142 271	49.1 73.7	2.9 3.7	64 100	45 37	0.93 0.77	97.6 97.7	5 —	40/7 —	31/13 52/26	21 40	— —	103/13 —	— —	112/71 —	90 100	— —	122/61	85 —	— —	1,280 1,510	300 450	— —	— —	9 —	49 —	49 —	— —	—

BSA = body surface area ($M.^2$).
S.R. = sinus rhythm.
A.F. = atrial fibrillation.
R = resting. E = exercise.
$\dot{V}_{O_2}$ = oxygen consumption (c.c./$M.^2$/min., STPD).
A-V O_2 diff. = arteriovenous difference (c.c./L.).
C.I. = cardiac index (L./$M.^2$/min.).
H.R. = heart rate (beats/min.).
S.I. = stroke index (c.c./$M.^2$/beat).
R.Q. = respiratory quotient.
Sa_{O_2} = arterial blood oxygen saturation.

RA = right atrial.
RV = right ventricular.
PA = pulmonary artery.
"PC" = pulmonary "capillary."
LV = left ventricular.
BA = brachial artery.
FA = femoral artery.
S = systolic. D = diastolic. M = mean.
SM = systolic mean.

TSR = total systemic resistance.
TPR = total pulmonary resistance.
PVR = pulmonary vascular resistance.
"LHR" = "left heart resistance."
MVA = mitral valve area.
AVA = aortic valve area.

MATERIAL AND METHODS

Thirty patients with various types of cardiovascular diseases were studied, including 10 patients with aortic stenosis, 5 with both mitral and aortic stenosis, 8 with mitral stenosis, and 7 with other cardiovascular diseases.

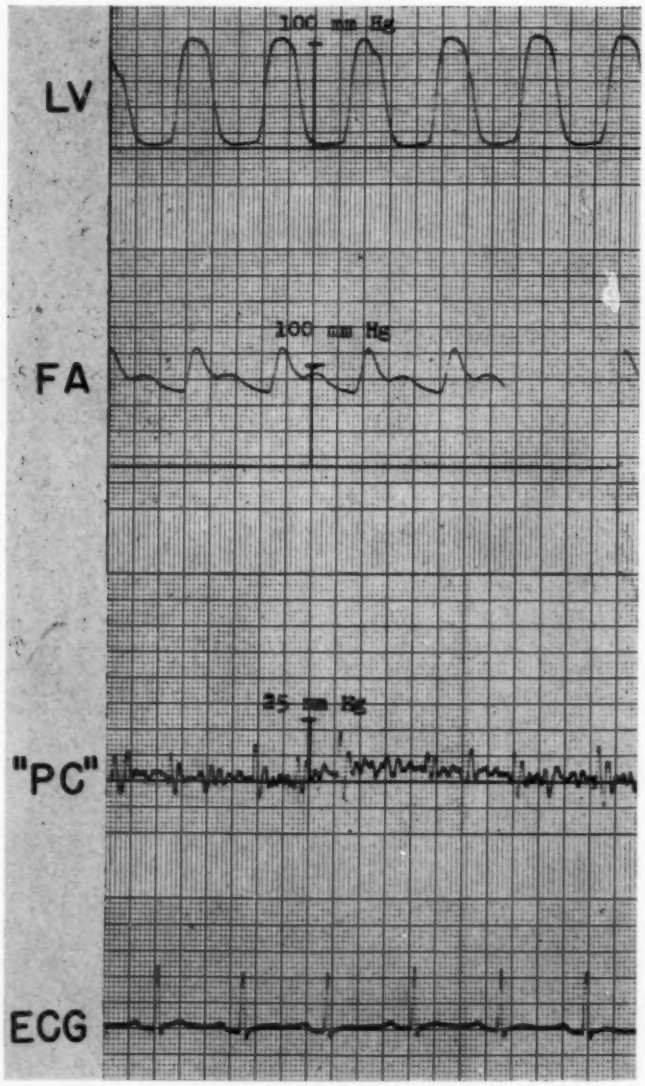

Fig. 1.—C. McL. Simultaneous left ventricular, brachial artery, and pulmonary "capillary" pressure tracings in a patient with mild congenital pulmonary stenosis. Note negative systolic pressure gradient from the left ventricle to the brachial artery. No significant diastolic pressure gradient exists across the mitral valve. In this and subsequent tracings the paper speed was 25 mm. per second, unless otherwise specified.

Right heart catheterization was carried out in the usual manner. A No. 7, long, Cournand catheter was introduced into a pulmonary artery, and a Riley needle was inserted into a brachial and/or a femoral artery. The oxygen consumption was initially estimated minute by minute from ventilation, measured by a wet test meter, multiplied by the difference between the oxygen con-

centration of the inspired and expired air, as determined by a Beckman oxygen analyzer. When the ventilation became stable, cardiac output was determined by the direct Fick principle with simultaneous sampling of expired air and arterial and mixed venous blood over a period of 2 minutes. The collected expired air was then analyzed by the Scholander technique, and the per cent

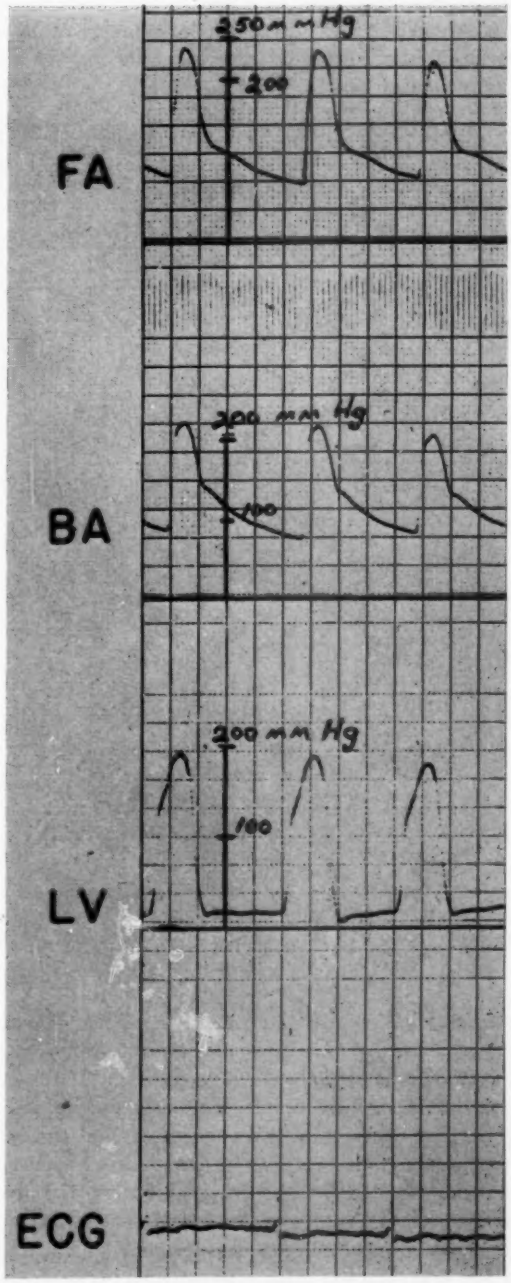

Fig. 2.—C. L. Simultaneous left ventricular, femoral artery, and brachial artery pressure tracings in a patient with hypertensive cardiovascular disease and probable aorticopulmonary fenestration. Note negative systolic pressure gradient from the left ventricle to the systemic arteries. The left ventricular diastolic pressure was elevated, indicating left ventricular failure.

of oxygen extracted was used for the final calculation of oxygen consumption, with ventilation corrected for respiratory quotient. Systemic and pulmonary artery pressures were recorded immediately after determination of cardiac output. In most instances, left ventricular puncture was carried out subsequently, and simultaneous pressures from the left ventricle and various vessels were obtained. In some cases, following control studies at rest, and prior to left ventricular puncture, comparative measurements of blood flow and pressure were made during the fifth minute of exercise. In the latter patients, direct left ventricular puncture was performed only when the heart rate and blood pressure had returned to resting values.

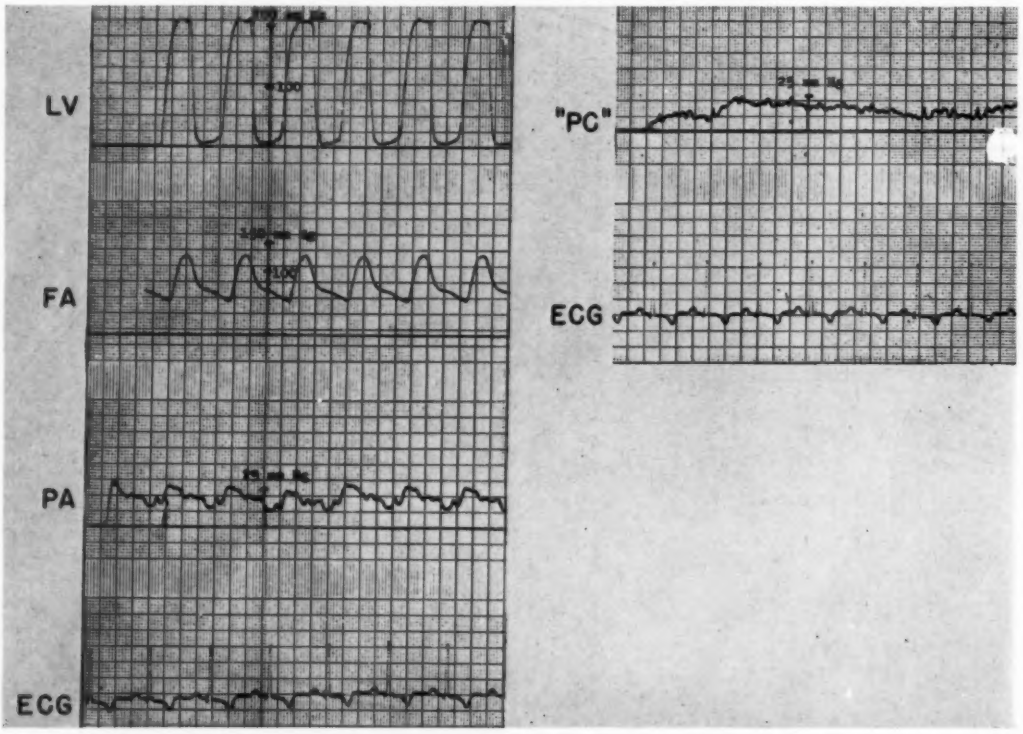

Fig. 3.—R. S. Moderate aortic stenosis. Left ventricular, femoral artery, and pulmonary "capillary" pressures were simultaneously recorded. Significant systolic pressure gradient from the left ventricle to the femoral artery was demonstrated and the left ventricular diastolic pressure was slightly elevated.

The following technique of left ventricular puncture, slightly modified from that described by Brock and associates,[11] was employed. With the patient supine, a point about 2 cm. below and lateral to the apical impulse was infiltrated with procaine. If the apical impulse was neither visible nor palpable, the cardiac apex was determined by fluoroscopy. An electrocardiogram was continually monitored throughout the entire procedure. When the infiltrating needle touched the myocardium, premature ventricular contractions frequently appeared, and the operator could feel the mass and movement of the left ventricle impinging upon the needle tip. At this moment the injection of procaine was discontinued and the needle withdrawn. A No. 19 gauge needle connected to an airtight 3-way stopcock and a syringe of heparinized saline was then inserted through the anesthetized site and directed along a line drawn between the second right costochondral junction and the apical impulse, with a posterior inclination of about 35 to 45 degrees. The needle was advanced gradually until the mass of the left ventricle was again felt. From this point the needle was advanced more rapidly until blood was aspirated in the syringe. This indicated that the ventricular cavity had been entered. Simultaneous blood samples were then obtained

from the chamber, pulmonary artery, and systemic artery. The duration of the puncture itself was usually not more than 5 minutes. Precautions were taken to avoid air embolism. During the procedure in our laboratory, an anesthesiologist and a thoracic surgeon were in attendance.

The level of all the gauges was set approximately 6.5 cm. below the angle of Louis. Pressures were recorded by Statham P23D strain gauges and a 4-channel Sanborn Poly-Viso recorder. Mean pressures were measured by planimetric or electronic integration.

Systemic and pulmonary resistances were calculated by the conventional formulae.[16] "Left heart resistance" includes resistance at the mitral valve as well as that of left ventricular filling.[17] It is the difference between total pulmonary resistance and pulmonary vascular resistance.

Aortic and mitral valve areas and ventricular stroke work against pressure were calculated according to the formulae proposed by Gorlin and co-workers,[18,19] and Sarnoff and Berglund.[20]

$$MVA = \frac{MVF}{31\sqrt{\text{"PC"}_m - LV_d}}$$

$$AVA = \frac{AVF}{44.5\sqrt{LV_{SM} - BA_{SM}}}$$

$$SW_{RV} = \frac{(PA_m - RV_d) \times S.I. \times 1.36 \times 1.055}{100}$$

$$SW_{TLV} = \frac{(LV_{SM} - LV_d) \times S.I. \times 1.36 \times 1.055}{100}$$

$$SW_{ELV} = \frac{(BA_{SM} - LV_d) \times S.I. \times 1.36 \times 1.055}{100}$$

Where:

MVA = mitral valve area (cm.^{2})
AVA = aortic valve area (cm.^{2})
SW_{RV}, SW_{TLV}, and SW_{ELV} = right ventricular, total left ventricular, and effective left ventricular stroke work, respectively (Gm.M./M.^{2}/beat)
MVF = mitral valve flow (c.c./sec.)
AVF = aortic valve flow (c.c./sec.)
BA_{SM} = brachial or femoral artery systolic mean pressure (mm. Hg)
LV_{SM} = left ventricular systolic ejection mean pressure (mm. Hg)
LV_d = left ventricular diastolic pressure (mm. Hg)
"PC"$_m$ = pulmonary "capillary" mean pressure (mm. Hg)
PA_m = pulmonary artery mean pressure (mm. Hg)
RV_d = right ventricular diastolic pressure (mm. Hg)
S.I. = stroke index (c.c./M.^{2}/beat)
1.055 = specific gravity of blood
1.36 = conversion factor from mm. Hg to cm. H_2O
31 and 44.5 = empirical constants.

RESULTS

Table I summarizes the heart rate, blood pressure, and arteriovenous oxygen difference during determination of cardiac output and during left ventricular puncture. Differences in heart rate and systemic artery pressure between the two periods of measurement were inconsistent and usually insignificant. Small variations were observed in the arteriovenous oxygen difference. These observations support the statement of Brock and associates[11] that left ventricular puncture does not usually alter the hemodynamics enough to affect the reliability of the information obtained.

The pressure tracings of 2 patients with neither aortic or mitral valvular disease are shown in Figs. 1 and 2. Their clinical history, physical findings, and physiologic studies are summarized as follows:

Patient C. McL., an 18-year-old male, had mild congenital pulmonary stenosis. He had had no physical disability. A Grade 3 systolic murmur and a Grade 1 diastolic murmur were heard at the pulmonic area, and the second pulmonic sound was normal. Cardiac catheterization disclosed no intracardiac shunt. Pulmonary artery pressure was normal and a systolic pressure gradient of 20 mm. Hg was demonstrated across the pulmonary valve. The left ventricular, femoral artery, and pulmonary "capillary" pressures were normal, and no pressure gradient across either aortic or mitral valve was observed (Fig. 1).

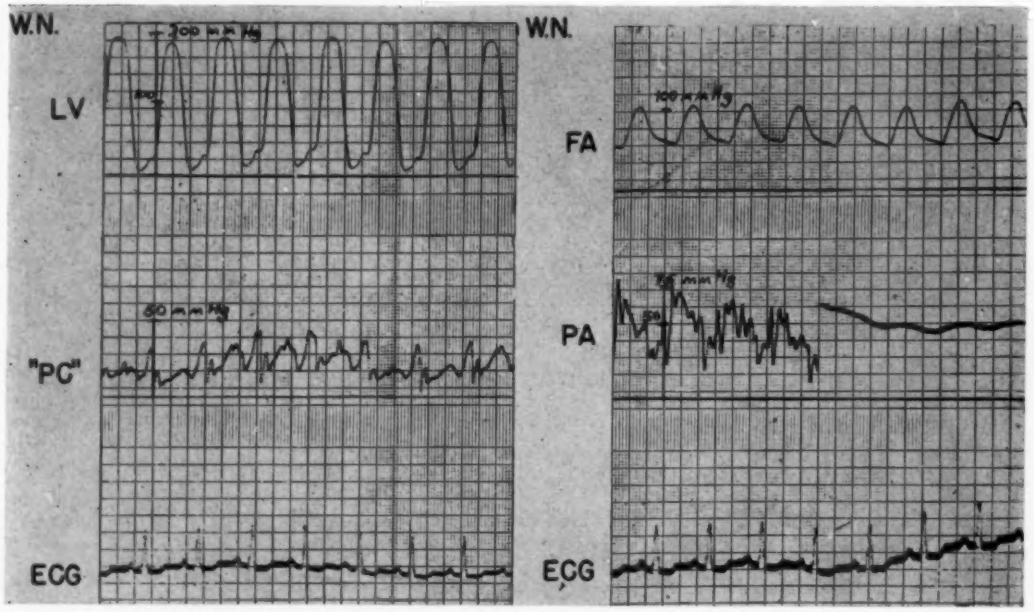

Fig. 4.—W. N. Severe aortic stenosis with left ventricular failure. Simultaneous left ventricular and pulmonary "capillary" pressures were measured immediately before simultaneous femoral artery and pulmonary artery pressures. Note the significant systolic pressure gradient from the left ventricle to the femoral artery. Markedly elevated left ventricular diastolic and pulmonary "capillary" pressures indicate severe left ventricular failure.

Patient C. L., a 46-year-old woman, had hypertensive cardiovascular disease and pulmonary hypertension secondary to a probable aorticopulmonary fenestration. Progressive exertional dyspnea and frequent episodes of paroxysmal nocturnal dyspnea had occurred. A loud continuous murmur was heard at the pulmonic area. Combined ventricular hypertrophy was demonstrated by electrocardiogram and fluoroscopy. Fig. 2 shows a negative systolic pressure gradient from the left ventricle to the systemic artery, a common observation in patients without aortic valvular disease. Systemic hypertension was present, and the left ventricular diastolic pressure was elevated.

Hemodynamic data from 8 representative patients with aortic and/or mitral stenosis are presented in Table II, and pressure tracings from 5 patients are il-

lustrated in Figs. 3 through 7. The clinical history, physical findings, and physiologic studies of these 8 patients are summarized as follows:

1. *Patients With Aortic Stenosis.*—

Patient R. S., a 38-year-old man, had "rheumatism" at age 11. No cardiac murmur was heard during a pre-employment physical examination at age 26, but 10 years later he was told that he had a loud cardiac murmur. For several years he had noticed some exertional dyspnea and easy fatigability. He had one syncopal attack 1 month prior to study. The physical signs were diagnostic of pure aortic stenosis. Electrocardiogram and fluoroscopy showed left ventricular hypertrophy. Physiologic studies demonstrated a significant systolic pressure gradient from left ventricle to femoral artery (Fig. 3). The left ventricular diastolic and pulmonary "capillary" pressures were slightly elevated.

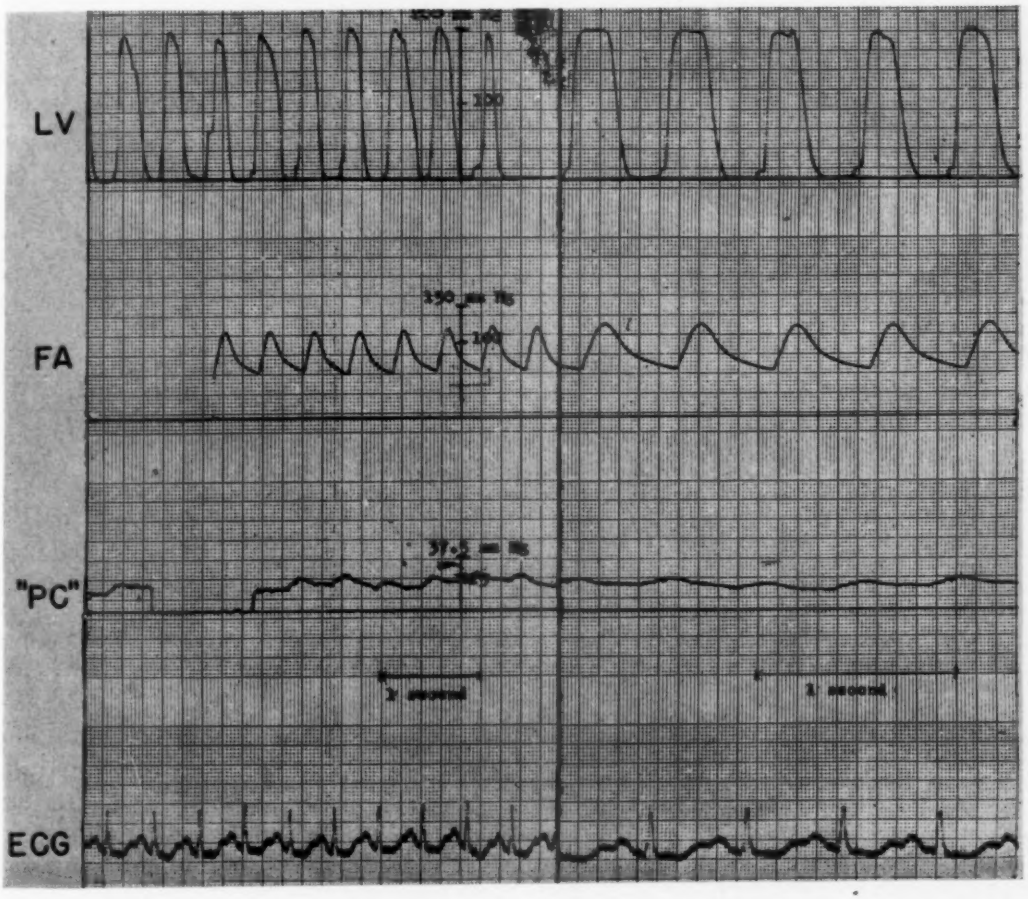

Fig. 5.—H. McD. Simultaneous left ventricular, femoral artery, and pulmonary "capillary" pressures in a patient with both aortic and mitral stenosis. Note the significant systolic pressure gradient from the left ventricle to the femoral artery, and the diastolic pressure gradient across the mitral valve. The left ventricular diastolic pressure was normal.

Patient W. N., a 47-year-old man, had dyspnea of increasing severity for 1 year. He had the classical physical signs of aortic stenosis. The electrocardiogram showed sinus rhythm and left ventricular hypertrophy. Radiologic examination disclosed left ventricular enlargement and a calcified aortic valve. Physiologic studies revealed an aortic valve area of 0.4 cm.^{2}, with a systolic

mean pressure gradient of 62 mm. Hg from the left ventricle to the femoral artery. Aortic blood flow was 125 c.c. per second. As shown in Fig. 4, severe left ventricular failure is indicated by markedly elevated left ventricular diastolic pressure (28 mm. Hg) and pulmonary "capillary" pressure (30 mm. Hg). At the time of aortic valvulotomy, marked aortic stenosis with extensive calcification was confirmed. The aortic valve area was estimated to be 0.3 cm.^{2}. Unfortunately, the patient died on the third postoperative day.

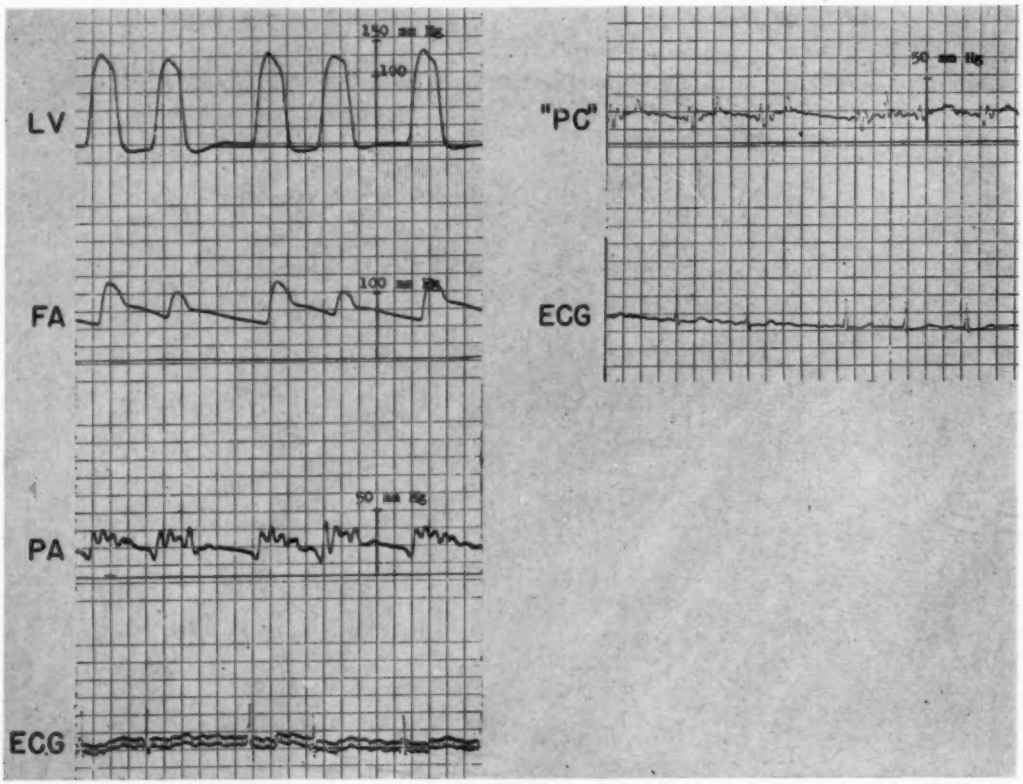

Fig. 6.—P. S. Simultaneous left ventricular, femoral artery, and pulmonary artery pressures followed by pulmonary "capillary" pressure in a patient with mitral stenosis. Note the significant diastolic pressure gradient across the mitral valve.

2. *Patients With Combined Aortic and Mitral Stenosis.—*

Patient H. McD., a 47-year-old housewife, had exertional dyspnea and increasing fatigability for about a year. Examination revealed the classical signs of both aortic and mitral stenosis. Fig. 5 illustrates the systolic pressure gradient from the left ventricle to the femoral artery, and the diastolic pressure gradient across the mitral valve. The aortic and mitral valve areas were calculated to be 0.5 cm.^{2} and 1.0 cm.^{2}, respectively. The left ventricular diastolic pressure was normal.

Patient A. B. presented similar clinical and physiologic findings, although mitral and aortic obstruction were less severe than in Patient H. McD.

3. *Patients With Mitral Stenosis.—*

Patient P. S., a 40-year-old man, had rheumatic fever at age 12. Easy fatigability and shortness of breath on exertion first developed at age 28. Ten years later he was given digitalis preparation for rapid heart action and dyspnea. On examination, the classical signs of mitral stenosis were present, while there was no evidence of aortic valvular disease. Fluoroscopic findings were consistent with mitral stenosis, and the electrocardiogram revealed atrial fibrillation and digitalis

effect. Combined left ventricular puncture and right heart catheterization disclosed a diastolic pressure gradient of 23 mm. Hg across the mitral valve (Fig. 6). There was a systolic pressure gradient of 4 mm. Hg across the aortic valve, which might have been due to slight pulse deficit secondary to fibrillation or mild aortic stenosis. The mitral valve area was estimated to be 0.8 cm.², and this was confirmed at surgery.

Patient B. M.'s physiologic data were comparable to those of Patient P. S. A diastolic pressure gradient of 15 mm. Hg was measured across the mitral valve. The valve area was estimated to be 1.0 cm.². There was no systolic pressure gradient demonstrable across the aortic valve.

4. *Patients With Mitral Stenosis and Myocardial Insufficiency.*—

Patient M. D., a 41-year-old woman with history of acute rheumatic fever at age 11, had exertional dyspnea, weakness, and easy fatigability for 6 years. On examination, the heart was considerably enlarged and there were physical signs of mitral stenosis. The electrocardiogram showed atrial fibrillation and no evidence of either right or left ventricular hypertrophy. Radiologic examination revealed an enormous heart with enlargement of all chambers as well as the pulmonary artery. Right heart catheterization was performed twice, and during the second catheterization left ventricular puncture was also performed. The hemodynamic studies were similar

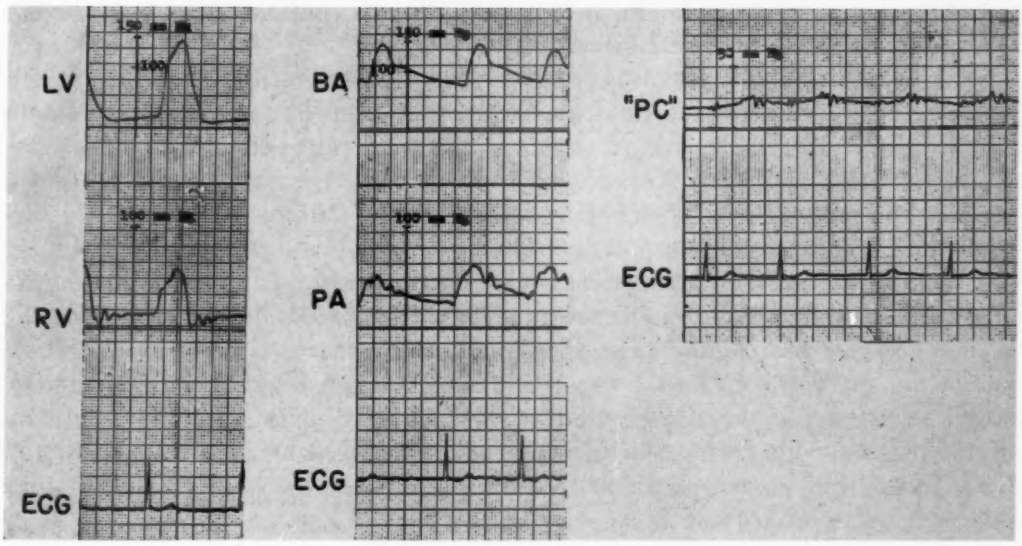

Fig. 7.—M. D. Rheumatic heart disease with mitral stenosis and myocardial insufficiency. The left and right ventricular pressures were recorded simultaneously, followed immediately by recording of simultaneous brachial and pulmonary artery pressures and pulmonary "capillary" pressure. The diastolic pressure in both the left and right ventricles was moderately elevated, and the diastolic pressure gradient across the mitral valve was only 5 mm. Hg. There was no systolic pressure gradient from the left ventricle to the brachial artery.

on both occasions. There was moderate pulmonary hypertension with elevated pulmonary "capillary" pressure (21 mm. Hg). As illustrated in Fig. 7, both left and right ventricular diastolic pressures were elevated (16 and 13 mm. Hg, respectively). The difference between the mean pulmonary "capillary" and left ventricular diastolic pressures was only 5 mm. Hg. The mitral valve area was calculated to be 1.1 and 1.2 cm.², respectively, in the two studies.

In Patient E. K., who also had classical signs of mitral stenosis, the left ventricular diastolic pressure was similarly elevated (13 mm. Hg). No pulmonary "capillary" pressure was recorded, but the mean pulmonary artery pressure was only 21 mm. Hg. It is reasonable to assume that the diastolic pressure gradient across the mitral valve was small.

COMMENTS

We fully agree with Brock and associates[11] that direct left ventricular puncture is a relatively simple and useful procedure for obtaining left ventricular pressure. Whenever the cardiac impulse is satisfactorily identified, the left ventricular cavity can be entered with ease. Following the technique described by these authors, we were successful in entering the left ventricular cavity in all but 1 of the last 26 patients. This patient had severe mitral stenosis and right ventricular hypertrophy, and the right ventricle was punctured instead of the left.

So far, we have observed no serious complications following the procedure. Several patients complained of severe local pain for a few days, and 3 developed a small apical pneumothorax. Teleroentgenograms of the chest taken about 3 hours after ventricular puncture showed no change in cardiac silhouette. In 3 patients, who a few weeks later had mitral commissurotomy, the surgeon was unable to find the puncture wound or any abnormality on the myocardium. We feel that this procedure should not be performed in patients with myocardial infarction or severe myocardial disease.

Right ventricular pressure may be markedly elevated in some patients with severe mitral stenosis. In such cases, the magnitude of the ventricular pressure may not indicate reliably which ventricle has been entered. Whenever such a question arises, immediate inspection and subsequent gas analysis of the blood samples simultaneously obtained from the ventricle, pulmonary artery, and systemic artery will resolve the uncertainty.

Systolic pressure in the left ventricle and in the aorta of normal subjects is equal, but systolic pressure in a peripheral artery (brachial or femoral) is, on the average, 10 per cent higher than that in the central artery (aorta).[3] It is not surprising, therefore, to find a negative systolic pressure gradient from the left ventricle to the peripheral artery in patients without aortic stenosis. One may state with confidence that a positive systolic mean pressure gradient of 10 mm. Hg or more from the left ventricle to the femoral artery probably indicates some degree of aortic stenosis.

Fleming and Gibson[12] found a fairly close correlation between the size of the aortic valve area calculated by hydraulic formula and that estimated at aortic valvulotomy. They believe that, provided there is no significant degree of aortic regurgitation, the calculated aortic valve area gives a reasonable estimate of the degree of aortic stenosis. This can be achieved by simultaneous measurement of the blood flow and systolic pressure gradient across the aortic valve. With a fixed valve area, the systolic pressure gradient depends upon the amount of stroke output; hence, the magnitude of the gradient alone may not be a reliable index in the assessment of the severity of the obstruction.

Clinical studies of patients with aortic stenosis[21,22] have shown that they may be arbitrarily classified into 3 groups: (1) mild, (2) moderately severe, and (3) severe. The clinical symptoms vary from virtually none in the first group to marked disability in the third.

Physiologic studies by other workers[12,19] have suggested that patients with mild or moderately severe aortic stenosis probably have an aortic valve area of

0.5 cm.^{2} or greater, and those with severe aortic stenosis usually have an aortic valve area less than 0.5 cm.^{2}. Many patients in the latter group may have manifestations of left and right ventricular failure. Our studies would indicate that the 3 patients with a calculated aortic valve area of less than 0.5 cm.^{2} did indeed have disability. In these patients the aortic valve flow was reduced and the left ventricular end-diastolic pressure moderately or markedly elevated. The total left ventricular stroke work was either normal or slightly decreased. In 7 patients with a calculated aortic valve area of 0.5 cm.^{2} or greater the aortic valve flow was usually normal, the left ventricular end-diastolic pressure either normal or only slightly elevated, and the total left ventricular stroke work moderately or markedly increased. A detailed report of the circulatory dynamics of aortic stenosis is in preparation.[23]

Measurement of left ventricular systolic and diastolic pressures yields valuable information regarding the relative severity of both lesions when aortic and mitral stenosis coexist. The severity of stenosis of either valve is grossly indicated by the magnitude of the pressure gradient across that valve, provided that significant aortic or mitral regurgitation is absent.

Since Gorlin and his associates[16] published their excellent studies of mitral stenosis in 1951, several reports of combined right and left heart catheterization have further elucidated the circulatory dynamics of this condition.[24-30] It is generally agreed that left ventricular diastolic pressure must be measured in order to estimate the mitral valve area more accurately. The usual assumption that left ventricular diastolic pressure approximates 5 mm. Hg will sometimes lead to significant underestimation of the valve area. Furthermore, without knowledge of left ventricular diastolic pressure it is not possible to assess the competence of the left ventricle separately from the effect of obstruction at the mitral valve.

In 1955, Harvey and associates[31] pointed out that significant myocardial insufficiency may be present in some patients with mitral stenosis. In these patients the results of mitral commissurotomy were usually disappointing. Recent studies in this laboratory with intravenous acetyl strophanthidin[32] suggested that hemodynamic responses in patients with pure mitral stenosis may differ from those in patients with mitral stenosis associated with myocardial insufficiency. In the present study it is possible to separate those patients with physical signs of mitral stenosis into 2 groups according to their left ventricular diastolic pressure. The larger group shows no demonstrable myocardial insufficiency (left ventricular diastolic pressure less than 10 mm. Hg); the smaller group has significant myocardial insufficiency (left ventricular diastolic pressure greater than 10 mm. Hg).

SUMMARY AND CONCLUSIONS

Thirty patients with various cardiovascular diseases were studied by Brock's method of anterior percutaneous left ventricular puncture combined with right heart catheterization and systemic artery puncture. Physiologic data from 8 representative cases are presented.

Pressure gradients and blood flow across both aortic and mitral valves may be estimated with reasonable accuracy by such methods, and valuable information regarding the severity of stenosis of the respective valve may be obtained.

In patients with aortic stenosis the critical level of the calculated aortic valve area seems to be 0.5 cm.^{2}. Patients with an aortic valve area of 0.5 cm.^{2} or greater usually have a normal or slightly reduced aortic flow, and normal or slightly elevated left ventricular end-diastolic pressure. The total left ventricular work is moderately or markedly increased.

In contrast, those with an aortic valve area of less than 0.5 cm.^{2} usually have a reduced aortic valve flow, and moderately or markedly elevated left ventricular end-diastolic pressure. In these patients the total left ventricular work is either normal or slightly decreased.

In patients with mitral stenosis the measurement of left ventricular pressure is particularly helpful in the evaluation of competence of the left ventricle and in the determination of the diastolic pressure gradient across the mitral valve. Based upon the magnitude of left ventricular diastolic pressure, separation of these patients into a larger group without myocardial insufficiency and a smaller group with myocardial insufficiency may be made. This separation has important clinical significance in the selection of certain patients for mitral valve surgery.

We agree with Brock and associates that direct puncture of the left ventricle through the anterior chest wall is a simple and useful method. It causes no significant hemodynamic alterations and so far has been devoid of serious complications.

We are indebted to the members of the Departments of Anesthesia and Surgery for their attendance during the procedure. We wish to express our appreciation to Mrs. Ruth Knight and Mrs. Susan Magruder for their technical assistance, and to Miss Irene Subrani for preparing the manuscript.

REFERENCES

1. Epps, R. G., and Alder, R. H.: Brit. Heart J. **15**:298, 1953.
2. Connolly, D. C., Tomkins, R. G., Lev, R., Kirklin, J. W., and Wood, E. H.: Proc. Staff Meet. Mayo Clin. **28**:72, 1953.
3. Kroeker, E. J., and Wood, E. H.: Circulation Res. **3**:623, 1955.
4. Wright, J. L., Toscano-Barboza, E., and Brandenburg, R. O.: Proc. Staff Meet. Mayo Clin. **31**:120, 1956.
5. Björk, V. O.: Acta chir. scandinav. **107**:466, 1954.
6. Fisher, D. L.: J. Thoracic Surg. **30**:379, 1955.
7. Morrow, A. G., Braunwald, E., Haller, J. A., and Sharp, E. H.: Circulation **16**:1033, 1957.
8. Ponsdomenech, E. R., and Nuñez, V. B.: Am. Heart J. **41**:643, 1951.
9. Smith, P. W., Wilson, C. W., Cregg, H. A., and Klassen, K. P.: J. Thoracic Surg. **28**:273, 1954.
10. Burch, G. E., Cronvich, J. A., Creech, O., and Hyman, A.: Am. Heart J. **53**:890, 1957.
11. Brock, R., Milstein, B. B., and Ross, D. N.: Thorax **11**:163, 1956.
12. Fleming, P., and Gibson, R.: Thorax **12**:37, 1957.
13. Bercu, B. A., and Diettert, G. A.: Newer Techniques for Left Heart Catheterization, Abstracts of the 30th Scientific Session, American Heart Association, October, 1957.
14. Bruce, R. A.: Personal communication.
15. Greene, D. G., Sharp, J. T., Griffith, G. T., Bunnell, I. L., and MacManus, J. E.: Surgery **43**:1, 1958.
16. Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W., and Dexter, L.: Am. Heart J. **41**:30, 1951.

17. Yu, P. N., Nye, R. E., Jr., Lovejoy, F. W., Jr., Schreiner, B. F., and Yim, B. J. B.: J. Clin. Invest. **37**:194, 1958.
18. Gorlin, R., and Gorlin, S. G.: AM. HEART J. **41**:1, 1951.
19. Gorlin, R., McMillan, I. K. R., Medd, W. E., Matthews, M. B., and Dailey, R.: AM. J. Med. **18**:855, 1955.
20. Sarnoff, S. J., and Berglund, E.: Circulation **9**:706, 1954.
21. Kumpe, C. W., and Bean, W. B.: Medicine **27**:139, 1948.
22. Bergeron, J., Abelmann, W. H., Vazquez-Milan, H., and Ellis, L. B.: A.M.A. Arch. Int. Med. **94**:911, 1954.
23. Yu, P. N., et al: Circulatory Dynamics of Aortic Stenosis Studied by Combined Left Ventricular Puncture and Right Heart Catheterization. (In preparation.)
24. Goldberg, H., Dickens, J., Raber, G., and Hayes, E., Jr.: AM. HEART J. **53**:579, 1957.
25. Fisher, D. L.: Retrograde Arterial Left Heart Catheterization, With Nonfluoroscopic Venous Right Heart Catheterization. Abstracts of the 30th Scientific Session, American Heart Association, October, 1957.
26. Lawrence, G. H., Zimmerman, H., Bercu, B., and Burford, T.: Surg., Gynec. & Obst. **101**:558, 1955.
27. Hecht, H. H., and Lange, R. L.: Circulation **14**:950, 1956.
28. Samet, P., Litwak, R., Bernstein, W. H., and Rosenthal, A.: Circulation **14**:995, 1956.
29. Fox, I. J., Wakai, C. S., Connolly, D. C., and Wood, E. H.: Proc. Staff Meet. Mayo Clin. **31**:126, 1956.
30. Dickens, J., Raber, G., Woldow, A., Lorange, G. C., and Goldberg, H.: New England J. Med. **256**:1017, 1955.
31. Harvey, R. M., Ferrer, M. I., Samet, P., Bader, R. E., Bader, M. E., Cournand, A., and Richards, D. W.: Circulation **11**:531, 1955.
32. Yu, P. N., Nye, R. E., Jr., Lovejoy, F. W., Jr., Macias, J. De J., Schreiner, B. F., and Lux, J. J.: AM. HEART J. **54**:235, 1957.

Book Reviews

CLINICAL ELECTROCARDIOGRAPHY, PART I: THE ARRHYTHMIAS. By Louis N. Katz, A.B., M.A., M.D., F.A.C.P., and Alfred Pick, M.D., Philadelphia, 1956, Lea & Febiger, 737 pages. Price $17.50.

This new publication which limits itself to the cardiac arrhythmias should properly be considered a new book and not a second edition of a volume now ten years old. It represents, uniquely, the only real attempt at comprehensive coverage of the disorders of the heart beat, and, accordingly, fulfills a need which no other text approaches.

Semantics in electrocardiography and in the field of arrhythmias, in particular, has always been a problem. It is an admitted problem in this publication. Whereas most clinical cardiologists have a familiarity with the term "interference-dissociation," this phenomenon is considered as incomplete A-V dissociation. The authors object to interference, a physiologic concept, being integrated with the concept of block, a pathologic abnormality of impaired conduction, even though both may produce dissociation of atria and ventricles. There is also evidence of bias, which is freely admitted, as regards the mechanism of ectopic premature beats. The authors favor re-entry as the mechanism, rather than repetitive response as the most common cause of ectopic premature beats. These qualifications are freely acknowledged, however, and do not detract from the usefulness of the book, once the authors' orientation is understood.

A most helpful feature of the volume is that the diagnostic features of arrhythmias are clearly blocked off so that the basic diagnostic criteria needed can be readily obtained without reading unnecessary qualifying material.

There is an excellent chapter on the recognition of arrhythmias at the bedside and in the electrocardiogram, dealing with some of the basic facts which should be common knowledge to every practicing physician.

Altogether, this volume fills a need not met by any other book on clinical electrocardiography. It is recommended for the beginner, as well as for the experienced electrocardiographer.

B. W. M.

LA BALLISTOCARDIOGRAPHIE (VALEUR PRATIQUE) [THE PRACTICAL VALUE OF BALLISTOCARDIOGRAPHY]. By Jean F. Merlen and Jean Desruelles, Paris, 1956, Expansion Scientifique Française, 206 pages and 108 illustrations.

The reviewer's lack of personal experience with ballistocardiography does not allow a precise, critical appraisal of this book. However, this ignorance makes for appreciation of the clear and effective presentation of the subject. In the first of three sections, the technique, the basic physics, the nomenclature, and the accepted conventions of the method are described. In the second part the authors discuss the relations between cardiodynamics and the quantitative ballistocardiogram, and also between the ballistocardiogram and rheocardiogram. The third section is devoted to the ballistocardiogram in pathologic states of the cardiovascular system. A well-classified, extensive bibliography indicates good integration of the work of others with the personal experience of the authors. The scope of the ballistocardiographic method is well defined; it is not due to replace any of the others already in use in the study of the cardiovascular system.

The style of writing makes for pleasant reading, and the book is highly informative.

P. D.

PREVENTION OF CHRONIC ILLNESS, VOL. 1. Commonwealth Fund Book, Cambridge, Mass., 1957, Harvard University Press.

Prevention of Chronic Illness is recommended to all members of the medical profession, especially those in practice who have to deal with the problem in the first instance. It is also recommended to social workers, nurses, and others of the medical team whose close contact with chronic sickness has made them realize its seriousness. There is a wealth of material which will be of value to all who are concerned with the wide ramifications of the problem.

The first of a series of 4 volumes on chronic illness, it deals principally with prevention. This includes averting the occurrence of disease, halting its progression, periodic health examinations and screening procedures to detect disease, the educating of health personnel and the public in concepts and methods of preventive medicine, and community planning for prevention. The second part of the book contains summaries of information on the prevention of selected chronic diseases. The diseases discussed are arthritis, blindness, cancer, cardiovascular diseases, cerebral palsy, diabetes, epilepsy, impaired hearing, mental illness, multiple sclerosis, poliomyelitis, syphilis, tuberculosis, and industrial diseases.

The definition of chronic disease which has been adopted is a broad one. It comprises all impairments or deviations from normal which have one or more of the following characteristics: are permanent; leave residual disability; are caused by nonreversible pathologic alteration; require special training of the patient for rehabilitation; may be expected to require a long period of supervision, observation, or care.

The enormity of the problem is shown by the estimation in 1950, that there were 28 million Americans suffering from disabling and nondisabling chronic disease or impairment. Because of the ever increasing number of such patients and their many requirements over a long period of time from doctors, nurses, and others of the medical team both in and out of hospital, chronic illness has become a crushing financial burden to the patient and to the community. Nationally considered, the loss in man hours of work because of chronic illness represents an economic loss of many hundreds of millions of dollars annually.

It is all the more necessary, therefore, that everything possible be done to prevent chronic illness, to recognize it in its incipient stage, and to bring to bear all our accumulated knowledge to cure it or, at least, arrest it. Prevention of long-term illness also requires the use of rehabilatative and other measures to reduce its severity, shorten its course, and restore the patient to health, employability or, at the very minimum, to a state where he may be able to look after himself.

The discussion is clear, precise, and although brief, sufficiently detailed to present an adequate account of the major causes of chronic illness. As already indicated, this is not a textbook of the prevention of chronic illness. It presupposes a knowledge of the chronic illnesses, their etiology, pathology, symptomatology, diagnosis, and treatment. It attempts, and succeeds admirably, to focus our interest on the all too often neglected aspect of prevention, so that we will be better able to play a more active and understanding role as physicians in meeting the challenge which chronic illness poses for us all.

P. W.

THE CLINICAL MANAGEMENT OF VARICOSE VEINS. By David Woolfolk Barrow, M.D., Ed. 2, New York, 1957, Paul B. Hoeber, Inc., 169 pages, 70 figures.

This is a splendid book. The clear, concise, yet amazingly thorough discussions reflect the author's extensive experience with venous disease. The early chapters on venous anatomy, physiology, and pathology are most lucid. The chapter dealing with complications is extremely valuable. There is no hint of redundancy, and nothing of importance is omitted. This is not just another compilation of facts from the literature—it is a well-written treatise which gives an often neglected subject the careful attention it deserves. It should be read from cover to cover by every physician who deals with varicose veins in the leg.

J. W. E.

INSUFFISANCE CARDIAQUE (CARDIAC FAILURE). By J. Lo Jacomo, Paris, 1957, Librairie Maloine, 392 pages.

This book belongs to a series of "Les Petits Precis," small handbooks of medicine. Its main purpose seems to be to afford the medical student a didactic text to aid in preparation for examinations. The author has gone beyond the range suggested by the title of the book and has reviewed the entire subject of cardiology. After all, it is not generally accepted that all cardiopathies lead to cardiac insufficiency unless a sudden fatal complication interrupts the normal evolution of the disease. It would seem that the author has been a regular visitor of Professor Jean Lenègre's clinic, for Lenègre's teaching appears to be the foundation of this text. The book could be useful to a student or a physician who wished to review the fundamentals of cardiology. It is to be noted that the book lacks a bibliography.

P. D.

LES ANGORS CORONARIENS INTRIQUES (Intricate Anginas of Coronary Disease). By Roger Froment and Andre Gonin, Paris, 1956, Expansion Scientifique Française, 173 pages.

This excellent, rather small, book fits the dedication of the authors, two physicians of Lyon, "to our Master, Dr. Louis Gallavardin whose intense interest in atypical cases of angina pectoris is merely extended by our studies." Intricate angina is defined as follows, "A pattern of cardiac pain characteristic of coronary artery disease in which anomalies of symptomatology or of evolution of symptoms appear to be definitely dependent on associated extracoronary artery disease." The authors trace their concept principally to the works of Louis Gallavardin, Sir James Mackenzie, and Ernest Boas.

In the first part of their treatise the authors describe their experiences with 30 cases which fit the diagnosis of intricate angina. The principal manifestations of the syndrome are described—neuro-coronary, vertebro-coronary, gastrointestinal-coronary, the rarer pneumo-coronary, and poly-coronary intrications. This chapter ends with a general summary of diagnosis and treatment of these conditions.

In the second, and smaller, portion of the book the authors are joined by Professor Jordon in describing experimental studies designed to throw some light on the complex intrication of pain when two "neighboring" abnormalities coexist. The third section is devoted to correlating clinical and experimental data so as to construct a unified concept of pathogenesis. This leads to a formulation of principles which govern coronary pain.

Inspired by Gallavardin, Professor Froment has steadfastly devoted himself to the study of coronary artery disease and has contributed much to this book. His associates, Dr. Gonin, the coauthor, and Drs. P. Bruel and R. Mornex made a careful selection of cases from Professor Froment's collection of clinical records and from the literature, in order to document these concepts of cardiac pain.

In the United States and in Canada, the cardiologist literally lives with coronary artery disease. We could add some similar and even more spectacular cases with electrocardiographic proof. This book does give guidance in assessing a clinical history so as to discover the evidence suggesting intrication. This reviewer is in agreement with the authors' ideas concerning the effectiveness of treating cervical disc disease and cholelithiasis.

This book should be carefully studied by all cardiologists and physicians interested in coronary artery disease. It represents closely knit thinking about these unusual patterns of coronary disease symptoms in which two or more sources of pain produce atypical syndromes. This book reflects clearly the virtue of French medicine which recognizes the value of good clinical history obtained by effectively guiding the patient.

P. D.

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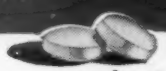

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[1]Fuller, H. L. and Kassel, L. E.: Antibiotic Medicine and Clinical Therapy, 3:322, October 1956.

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Wilkins, R. W.: New England J. Med. 257:1026, Nov. 21, 1957.

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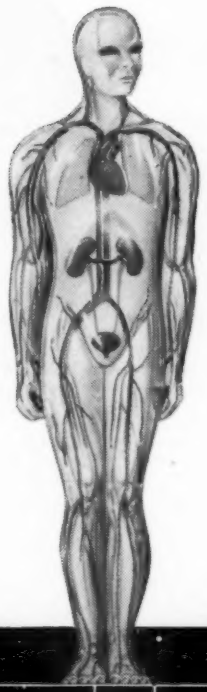

Freis, E. D., Wanko, A., Wilson, I. H. and Parrish, A. E.: J.A.M.A. 166:137, Jan. 11, 1958.

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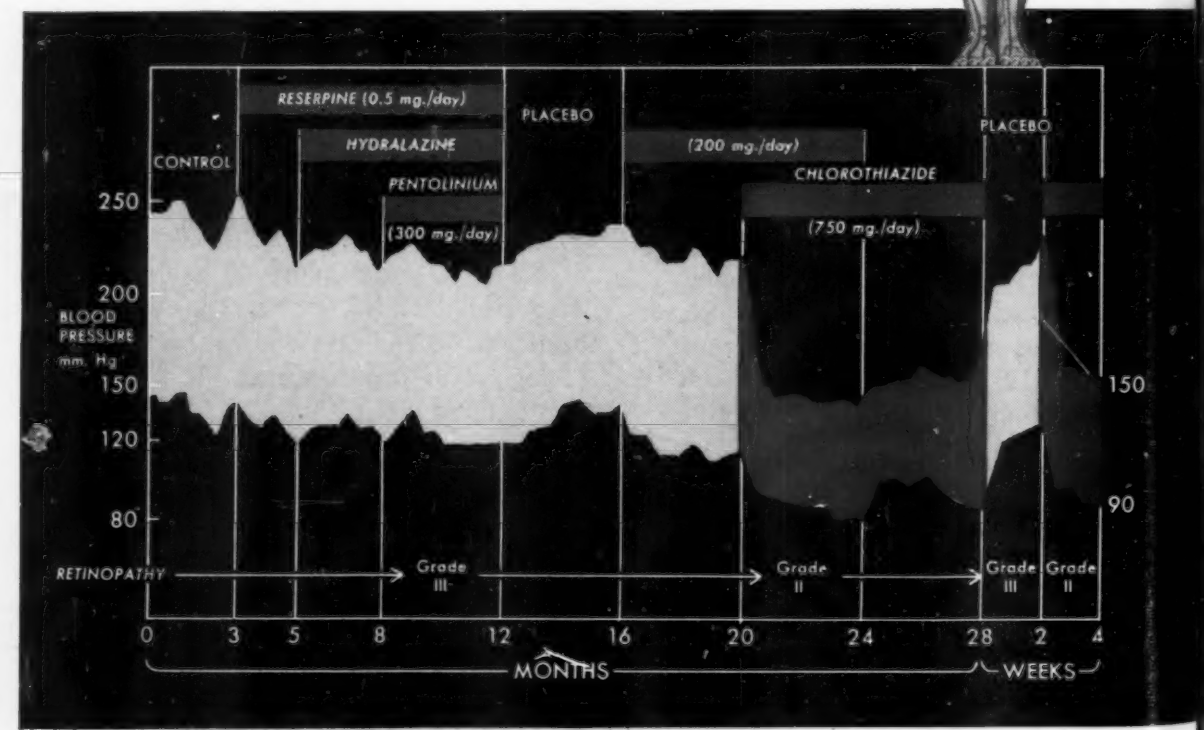

In "Chlorothiazide: A New Type of Drug for the Treatment of Arterial Hypertension," Hollander, W. and Wilkins, R. W.: Boston Med. Quart. 8: 1, September, 1957.

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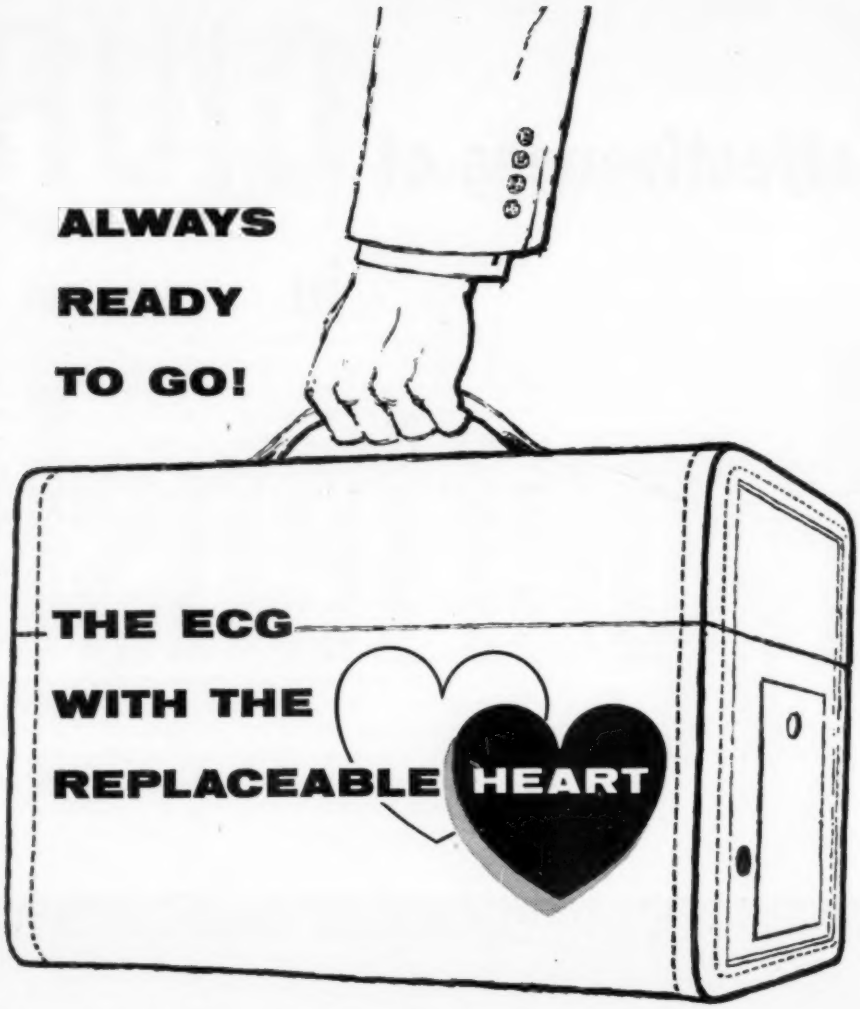

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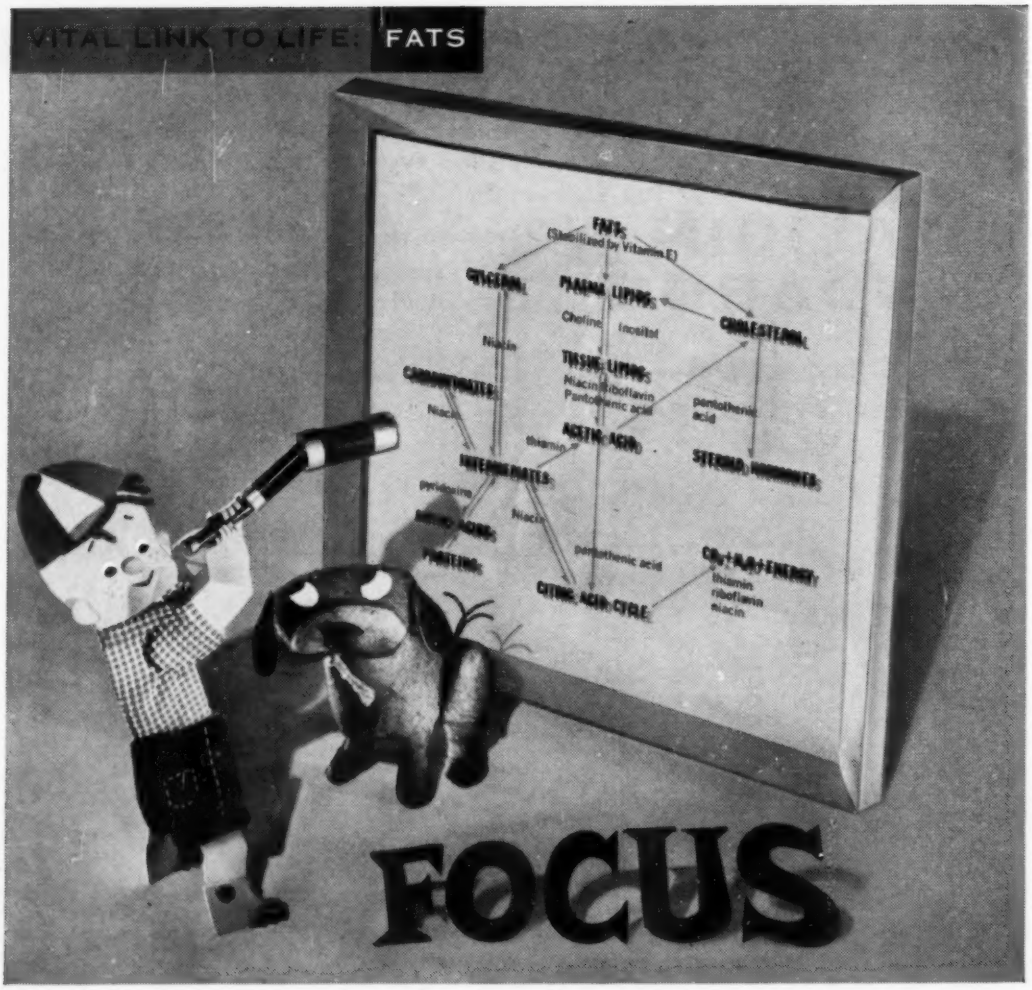

Acetic acid . . . a fatty acid . . . plays a central role in the interaction of nutrients required for synthesis of body tissues . . . maintenance of body warmth . . . and performance of work.

Fats, carbohydrates and proteins all contribute to the metabolic pool of acetic acid which can then be oxidized to carbon dioxide and water with release of energy for body use . . . or can be used for the synthesis of body substances such as cholesterol . . . hormones . . . tissue proteins . . . and fat for storage depots. Vitamins, minerals and proteins in enzyme systems cooperate to sever or join the chemical entities which make up functioning body tissues and yield energy as needed:

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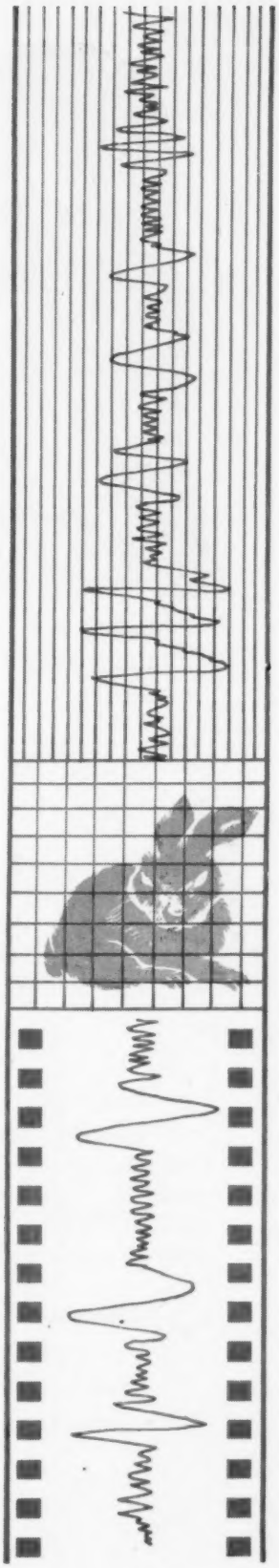

In angina pectoris

Relax the grip of fear and pain

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TYMCAPS

Feinblatt,* reporting on COROVAS' disintegration pattern and therapeutic effect in the New England Journal of Medicine, states:

0-3 hours – "During the first hour . . . no significant change in pain level . . . during the second hour most patients experienced a gradual diminution of pain. But at the end of the third hour all patients . . . had significantly less pain."

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With your angina patients you will discover – as Feinblatt found – that COROVAS Tymcaps relax the grip of pain and fear . . . all day and all night – day after day.

Formula: Each continuous release COROVAS Tymcap contains:
pentaerythritol tetranitrate (PETN) ..... 30 mg.
secobarbituric acid ..... 50 mg.

Dosage: 1 COROVAS Tymcap on arising – 1 COROVAS Tymcap before the evening meal, approximately 12 hours later.

Supply: COROVAS Tymcaps – boxes of 60 and 120.

*Feinblatt, T.M. and Ferguson, E.A.: New Eng. J. of Med. (Feb. 21) 1957.

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its high corn oil content will not elevate blood cholesterol levels

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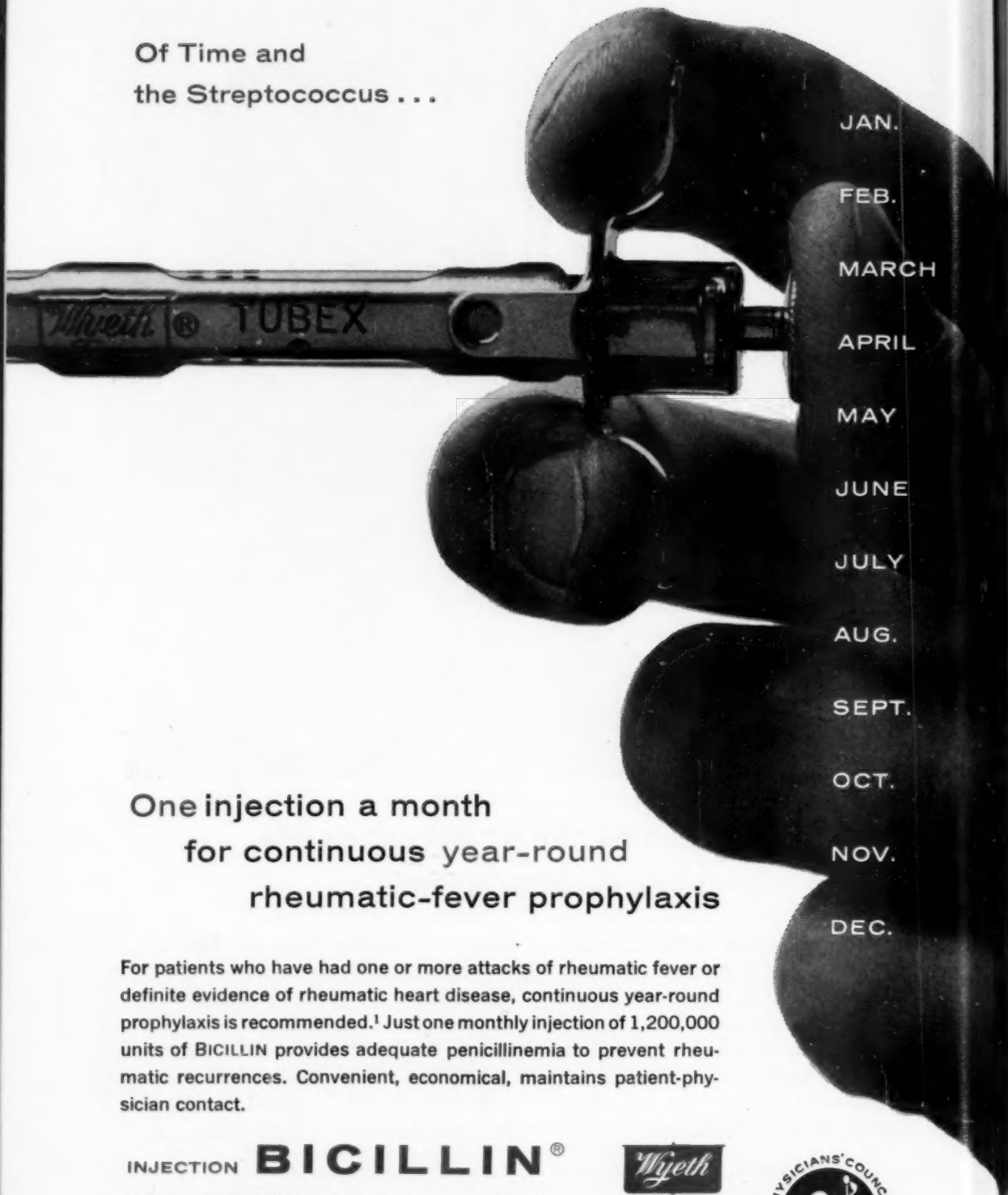
Of Time and
the Streptococcus . . .



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for continuous year-round
rheumatic-fever prophylaxis

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1. American Heart Association: Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis: Circulation 15:154 (Jan.) 1957.

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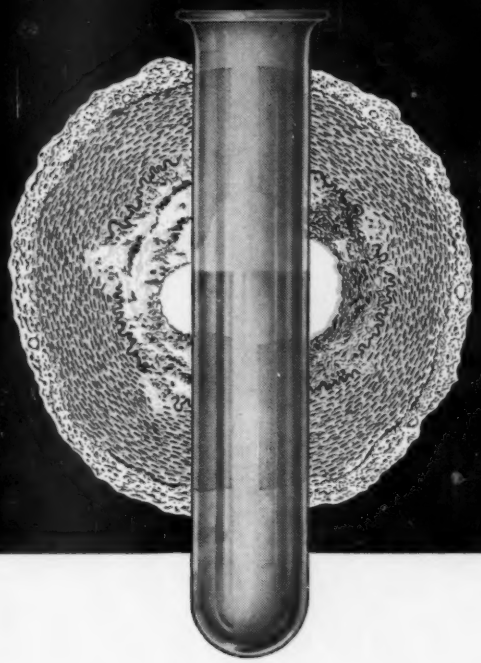
IN DIABETES

Blood Cholesterol Regulation Is Desirable



Frequently, diabetes mellitus is associated with excessive coronary atherosclerosis and heart disease. It is also well recognized that vascular disease manifests itself at an earlier age and progresses more rapidly in the diabetic . . . especially the diabetic female. The early onset and severe degree of atherosclerosis may be due to faulty lipid metabolism, with a concomitant elevation in blood cholesterol levels. Kinsell[1] reports that even in diabetics with extensive vascular disease it is possible to produce normal cholesterol levels with an essential fatty acid emulsion.

The consensus of opinion today is that elevated cholesterol levels should be reduced or prevented. This can be done very well by the addition of adequate amounts of linoleic acid and vitamin B_6 to the diet. In scores of diabetic patients, with extensive vascular disease, diets high in linoleic acid resulted in improvement.[2,3] Vitamin B_6 apparently is necessary to convert linoleic acid into the primary essential fatty acid, arachidonic acid. Thus the body is dependent on an intake of both linoleic acid and vitamin B_6 for normal cholesterol levels.[4,5]

This is why ARCOFAC (Armour Cholesterol Lowering Factor) provides *both* linoleic acid and vitamin B_6 in adequate amounts, thus allowing the patient to eat a balanced, nutritious and palatable diet. Prophylactic dosage is 1-2 tablespoonfuls daily; therapeutic—2-8 tablespoonfuls daily.

Each tablespoonful (15 ml.) of Arcofac emulsion contains:

Essential fatty acids†.....6.8 Gm.
(measured as linoleic) with 2.5 I.U. of Vitamin E*

Pyridoxine hydrochloride
(Vitamin B_6).....1.0 mg.

† Supplied by safflower oil which contains the highest concentration of polyunsaturated fatty acids of any commercially available vegetable oil.

*Added as Mixed Tocopherols Concentrate, N.F.

References 1-5 supplied on request.

Arcofac®

Armour Cholesterol Lowering Factor

THE ARMOUR LABORATORIES
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When "Breakfast Anorexia" must be Overcome

Anorexia upon arising must often be dealt with as part of a therapeutic regimen. In addition to the well-known syndrome of early pregnancy, several other causes of "breakfast anorexia" are recognized. Generally psychological in character, they include fear or lack of enthusiasm in facing the day, distaste or intolerance for the fried and fatty foods commonly served at breakfast, and habit patterns such as late rising with the inevitable morning rush. Obese patients who "cannot" eat breakfast tend to overeat during the day in order to overcome the deficit.

When "breakfast anorexia" must be overcome, physicians find that a dish of steaming oatmeal as the main food at breakfast is a great help in the solution of this problem. Its inviting warmth and delicious taste make the oatmeal dish appealing even when appetite is poorest. It also provides readily available energy for a morning of productive work; it helps to allay hunger throughout the morning; it makes a notable contribution to the day's nutritional needs; it is low in fat, and is easily digested.

Oatmeal is richer in protein than all other whole-grain breakfast cereals. It ranks among the highest in thiamine, and contributes other B vitamins as well. It is outstanding for its iron content.

The correction of "breakfast anorexia" can be made easier in many ways by a morning dish of oatmeal and milk, so quickly and easily prepared, and so gratifying.

Quaker Oats and Mother's Oats, the two brands of oatmeal offered by The Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

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whenever digitalis is needed

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"If one digitalis agent were to be recommended for its adaptability to the many and varied clinical contingencies, we believe Digoxin would be the drug of choice."

Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

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0.05 mg. in 1 cc.*

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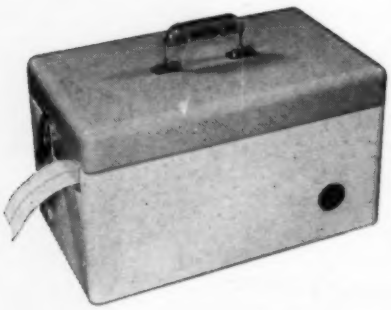

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for prophylaxis in angina pectoris

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The patient can better handle the stress of increased *effort* because pentaerythritol tetranitrate is a component in your prescription. This safe, long-acting, well-tolerated coronary vasodilator improves the blood flow through the coronary arteries.

And the patient is protected against *emotional factors* by the reliable sedative action of BUTISOL, combined with the mild, safe, tranquilizing effect of small doses of reserpine.

Each scored, pink tablet contains:

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Dosage: The usual dosage is one tablet four times a day administered *before* meals and at bedtime.

Note: PENTRALINE is not intended for treatment of acute attacks of angina pectoris, but rather for routine daily use as a preventive measure.

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and the identifiable biologically-active components of citrus

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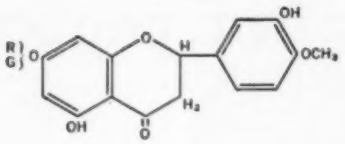

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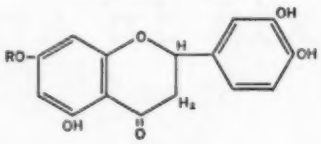

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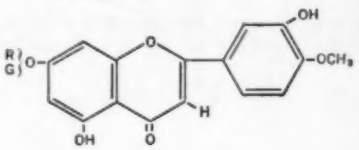

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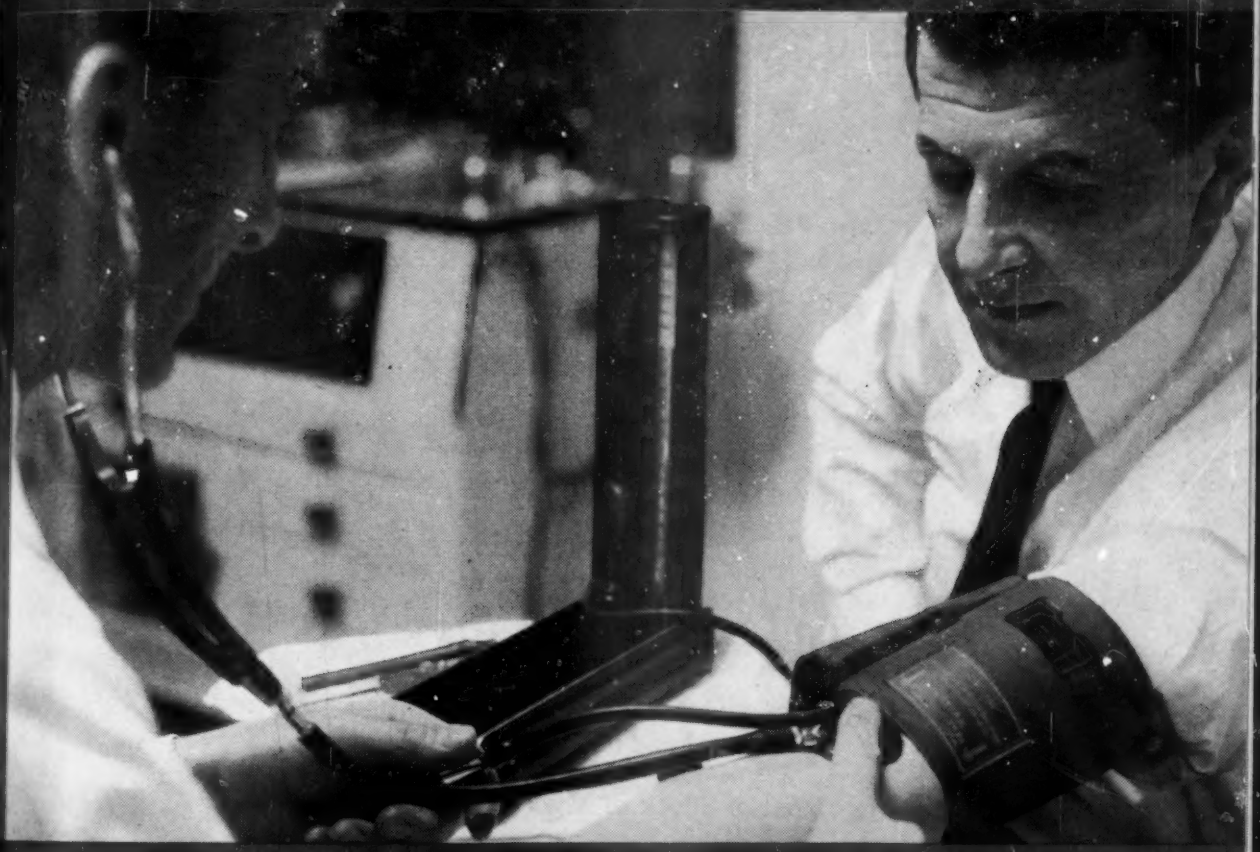
REFERENCES:

1. Javert, C. T., Ann. N. Y. Acad. Sci. 61, 700 (1955).
2. Greenblatt, R. B., Obst. Gyn. 2, 530 (1953).
3. Dill, L. V., Med. Ann. Dist. of Columbia, 23, 667 (1954).
4. Jacobson, B. D., Obstet. Gyn. 10, 40 (1957).
5. Rinehart, J. F., Ann. Rheumatic Diseases 5, 11 (1945).
6. Rinehart, J. F., Ann. N. Y. Acad. Sci. 61, 684 (1955).
7. MacLean, A. L. Read at General Clinical Sessions of Ophth. and Otolar., Southern Med. Assoc. (Nov. 24, 1947) Baltimore, Maryland
8. Dresner, J. L., Am. Pract. Dig. Treatment 6, 912 (1955).
9. Warter, P. J., et al, Del. State Med. J. 20, 41 (1948).
10. Boines, G. J., Ann. N. Y. Acad. Sci. 61, 721 (1955).
11. Dietz, N., Jr., Ind. Med. Surg. 26, 229 (1957).
12. Macon, W. L., Jr., Ind. Med. Surg. 25, 525 (1956).
13. Martin, G. J., et al., Exp. Med. Surg. 12, 525 (1954).
14. Fostvedt, G. A., Nut. Res. 12, 1 (1956).
15. Beiler, J. M. and G. J. Martin, J. Biol. Chem. 171, 507 (1947).
16. Bhagvat, K., Ind. J. Med. Res. 34, 87 (1946).
17. Fuhrman, F. A., Am. J. Physiol. 181, 123 (1955).
18. Ambrose, A. M. and N. P. Plotnikoff, Fed. Proc. 15, 1283 (1956)
19. Bacharach, A. L. and M. E. Coats, J. Soc. Chem. Ind. 63, 198 (1944).
20. Horne, G. and H. Scarborough, Lancet 2, 66 (1940).

When anxiety and tension complicate HIGH BLOOD PRESSURE



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1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. Am. J. M. Sc. **234**: 150, Aug. 1957.

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1. Russek, H. I.: Postgrad. Med. *19*:562 (June) 1956.

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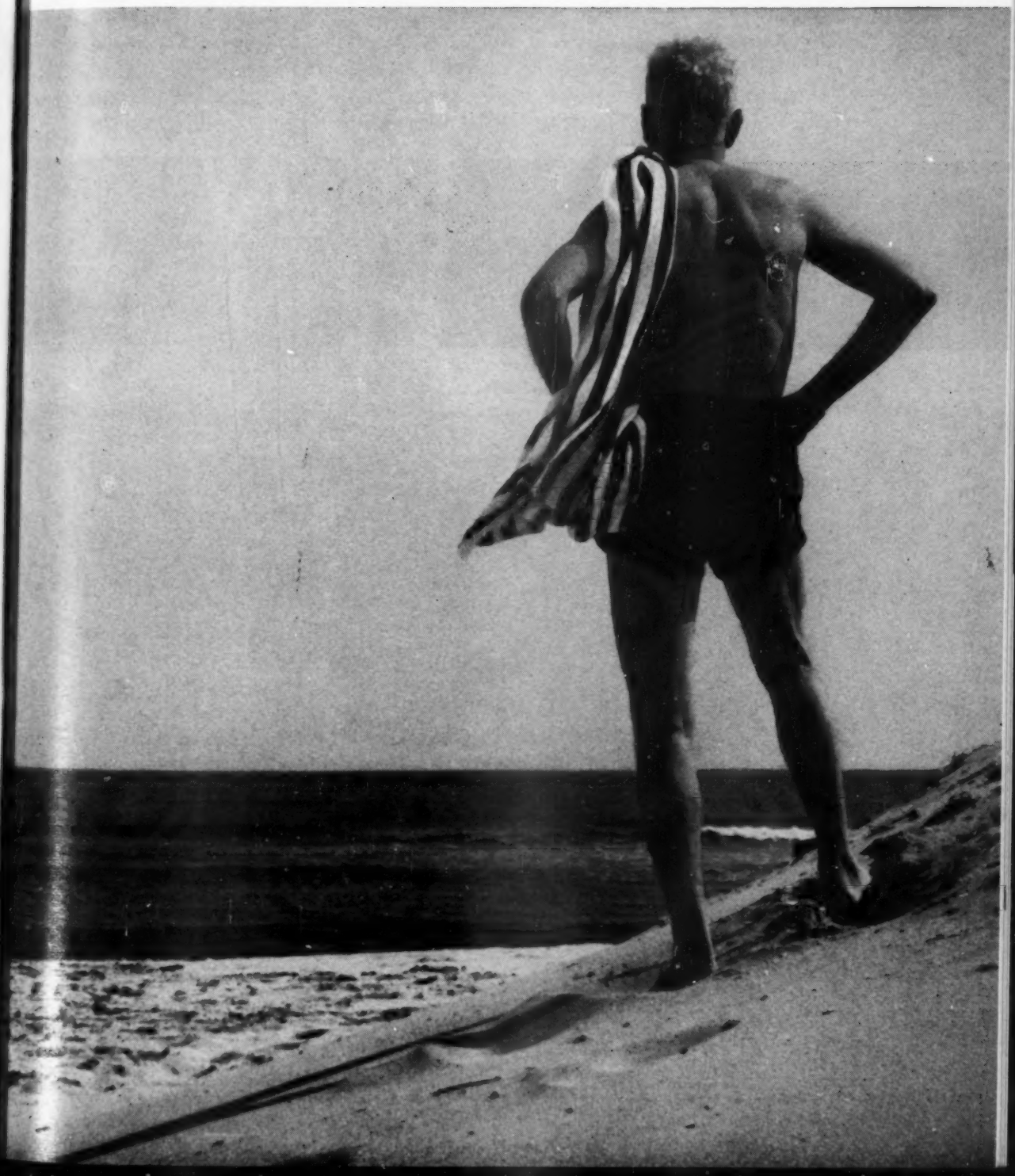

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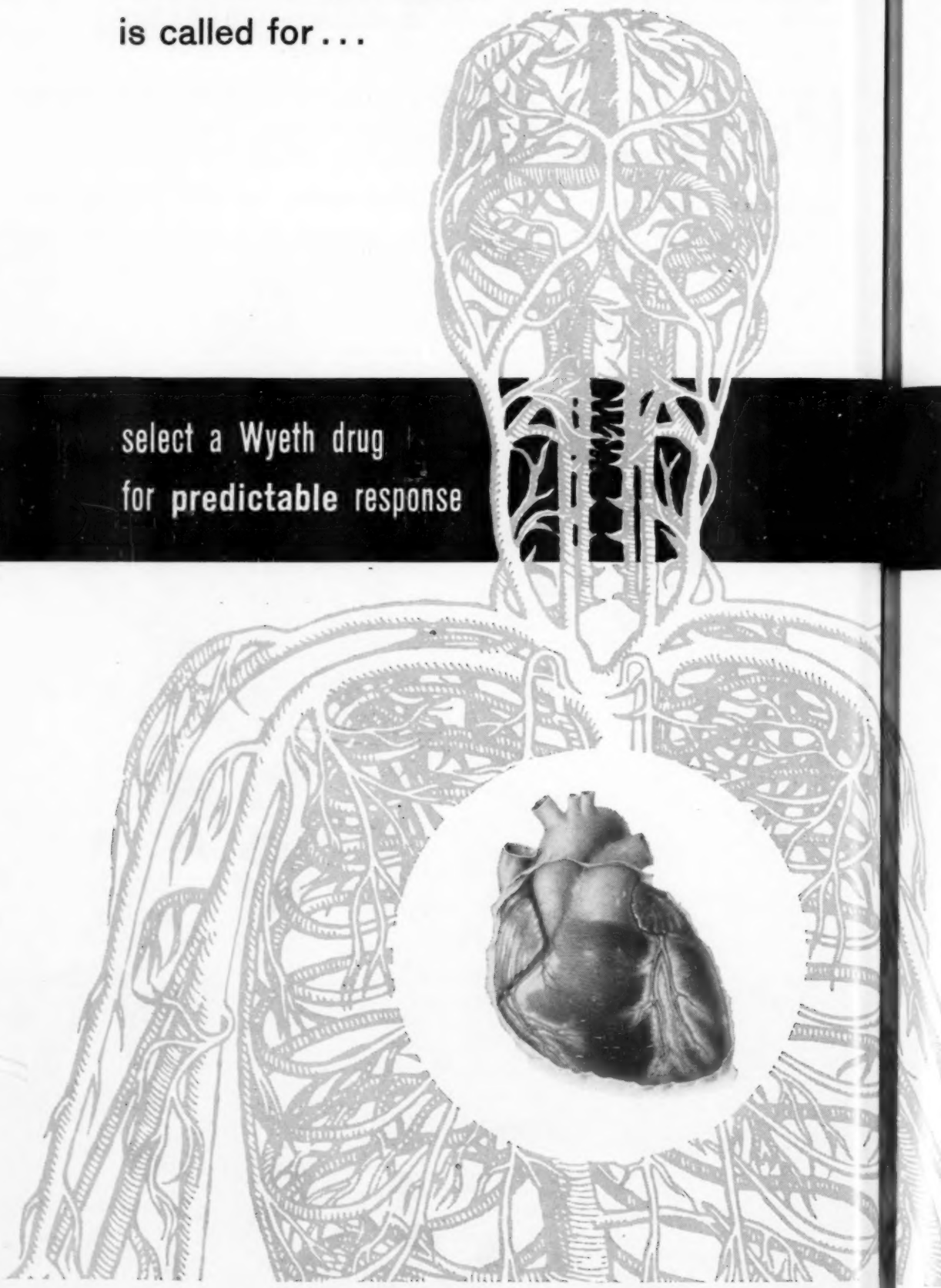

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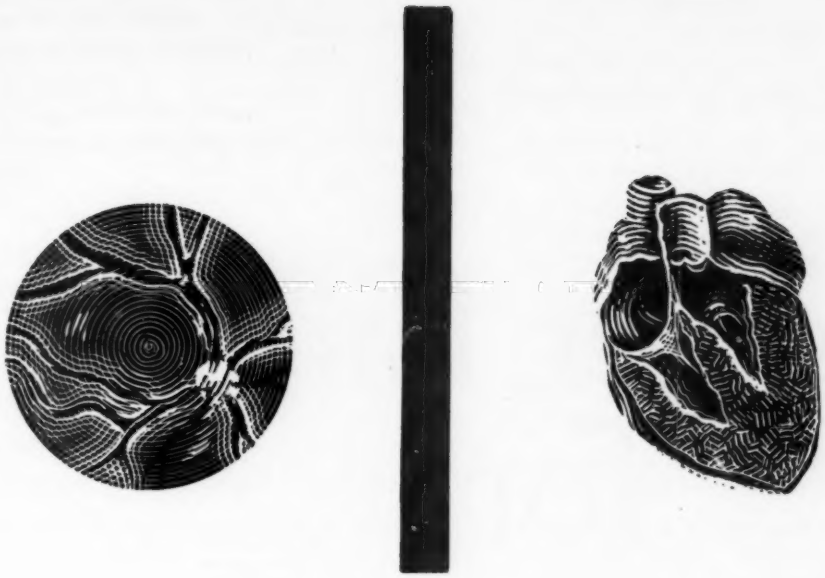

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Crawley, C. J. *et al*: N. Y. State J. of Med. 55:*23* (Dec.1) 1955: pp. 3461-3463.

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Council on Pharmacy and Chemistry, New and Nonofficial Remedies: Mecamylamine Hydrochloride, J.A.M.A. 162: 1469-1471, Dec. 15, 1956.

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3. *Adjust dosage of 'Diuril' for optimal response.*

Patients on 'Inversine' and/or other ganglionic blocking agents

1. *Initiate 'Diuril' therapy*

'Diuril' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

2. *Adjust dosage of ganglionic blocking agent*

If the patient is established on a ganglionic blocking agent (e.g., 'Inversine') it should be continued, but the total daily dosage should *immediately* be reduced by as much as 25 to 50 per cent. This will reduce the serious side effects often observed with ganglionic blockade.

If other antihypertensive agents are used, their dosage should be adjusted as indicated by patient response.

3. *Determine optimal maintenance dosage*

The patient *must* be observed frequently and careful adjustment of all agents should be made to determine optimal maintenance dosage.

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Riseman, J. E. F., Altman, G. E., and Koretsky, S.: Nitroglycerin and Other Nitrites in the Treatment of Angina Pectoris, Circulation (Jan.) 1958.

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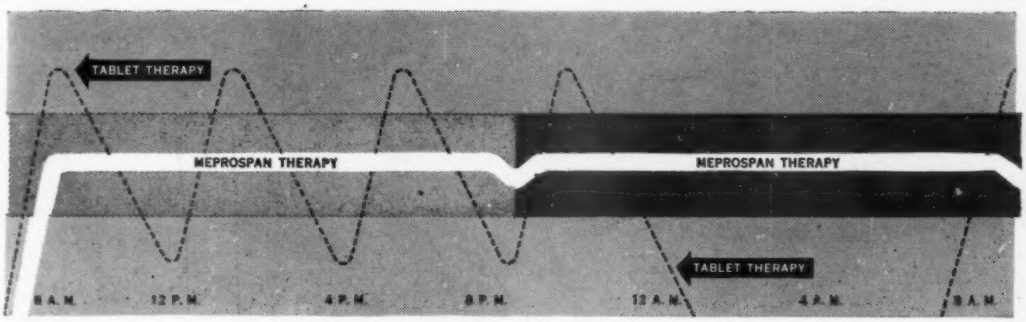

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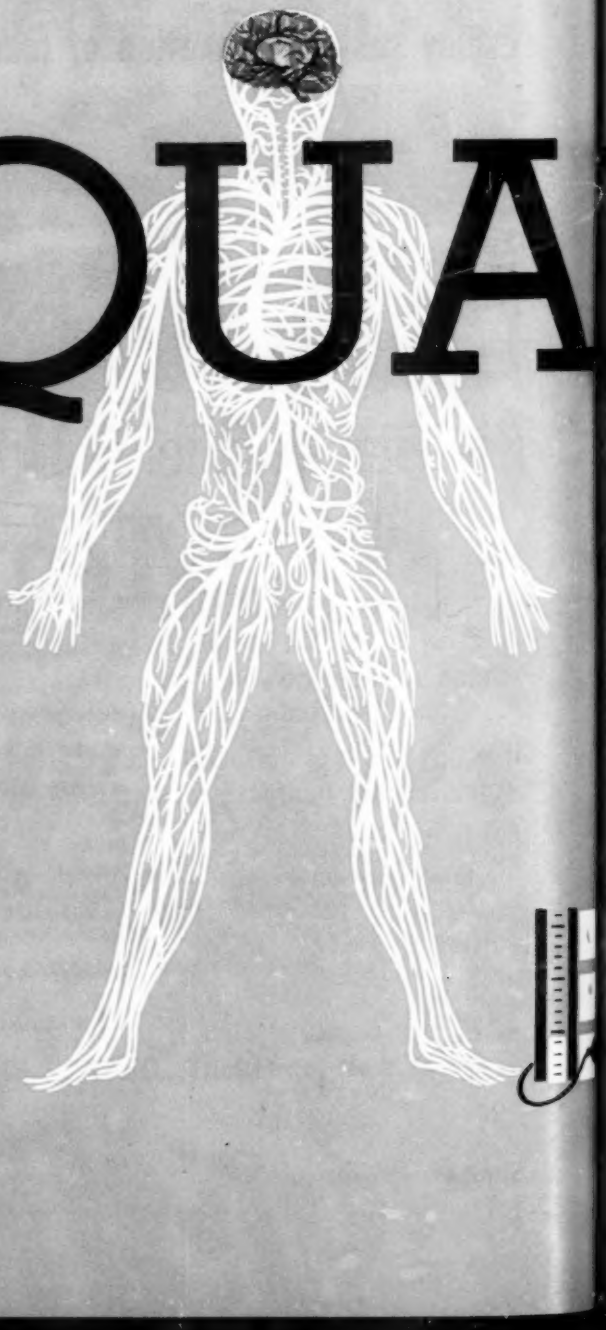

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1 Fulton, L.A., et al.: Am. Pract. & Digest Treat. *8*:1376 (Sept.) 1957.

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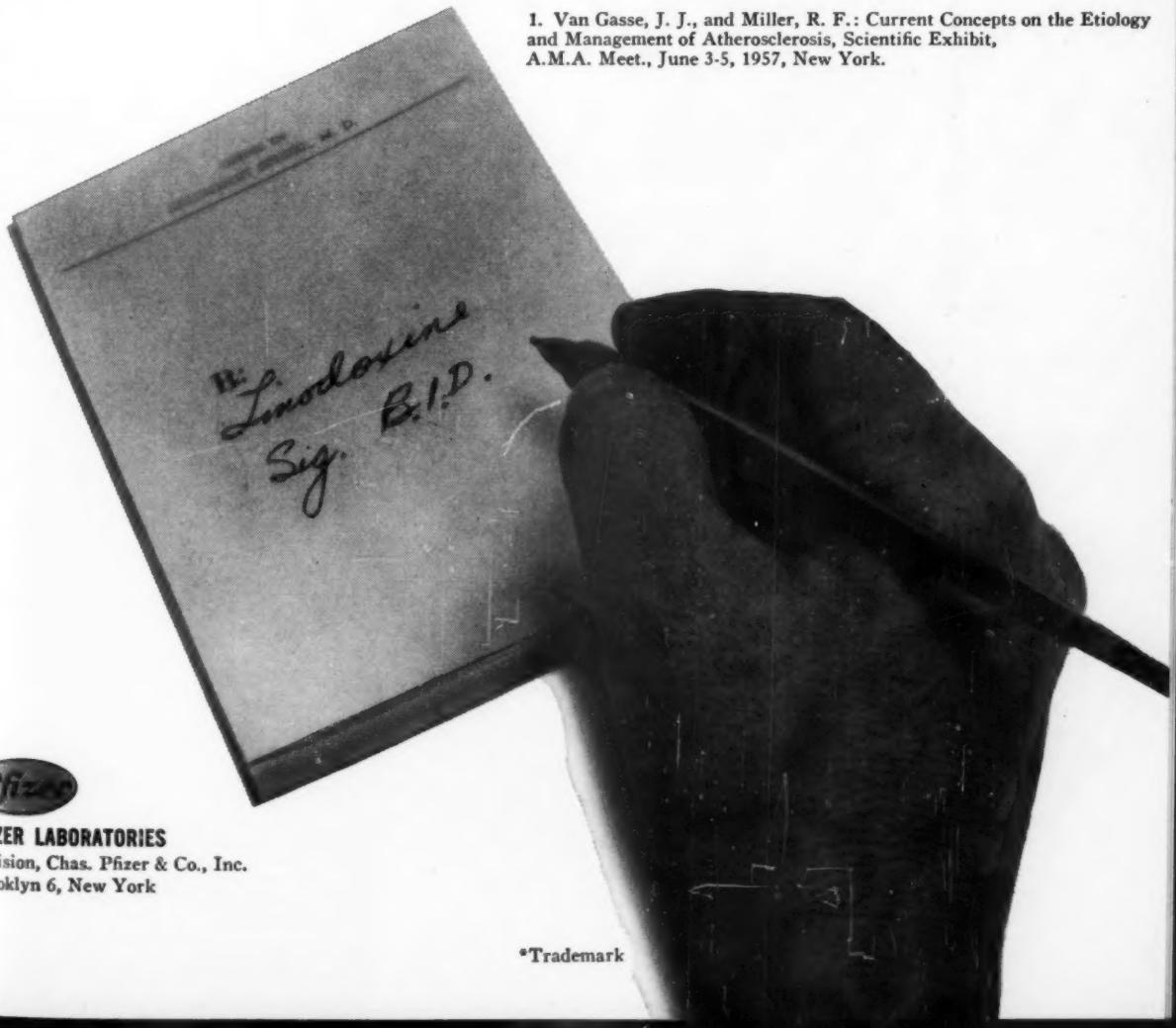
1. Van Gasse, J. J., and Miller, R. F.: Current Concepts on the Etiology and Management of Atherosclerosis, Scientific Exhibit, A.M.A. Meet., June 3-5, 1957, New York.



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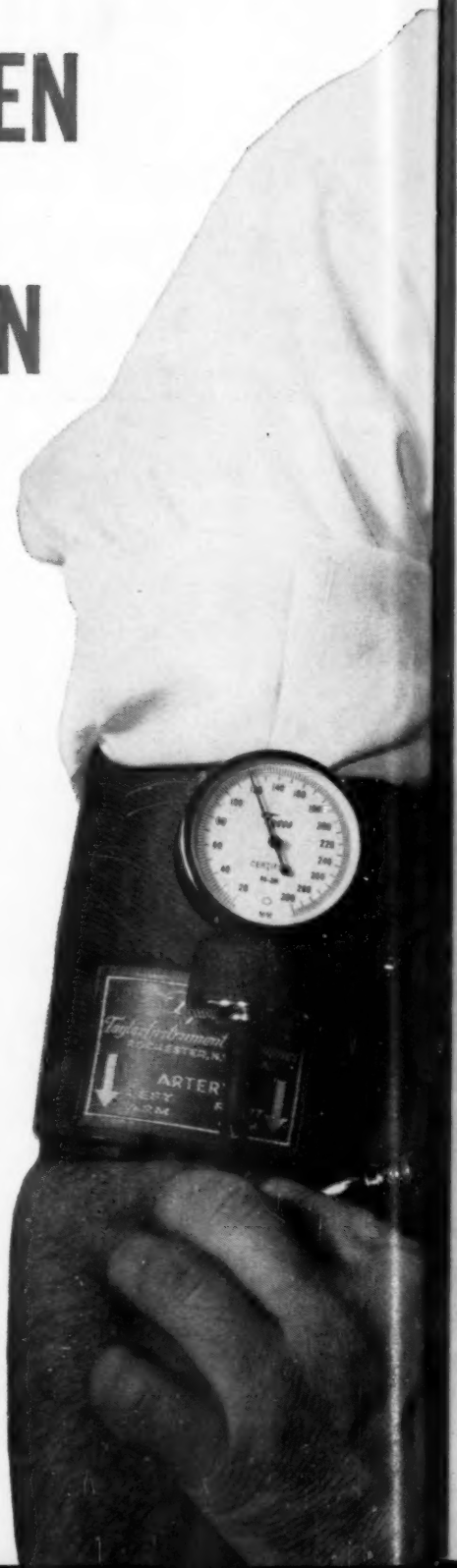

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1. Moyer, J. H., et al.: South. M. J. 50:499, 1957. 2. Smirk, F. H., and McQueen, E. G.: Lancet 2:119, 1955. 3. Winton, S. S.: Internat. Rec. Med. 170:665, 1957. 4. Malamud, W., et al.: Am. J. Psychiat. 114:193, 1957.

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1. Wright, I. S.: Early use of anticoagulants in treatment of myocardial infarction, J.A.M.A. 163: 918-921, March 16, 195
2. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505.

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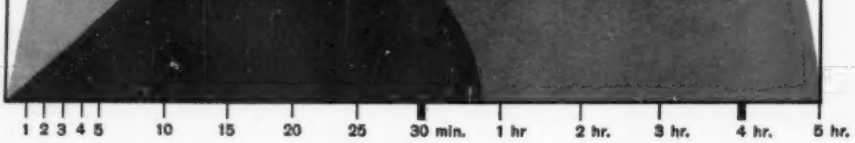

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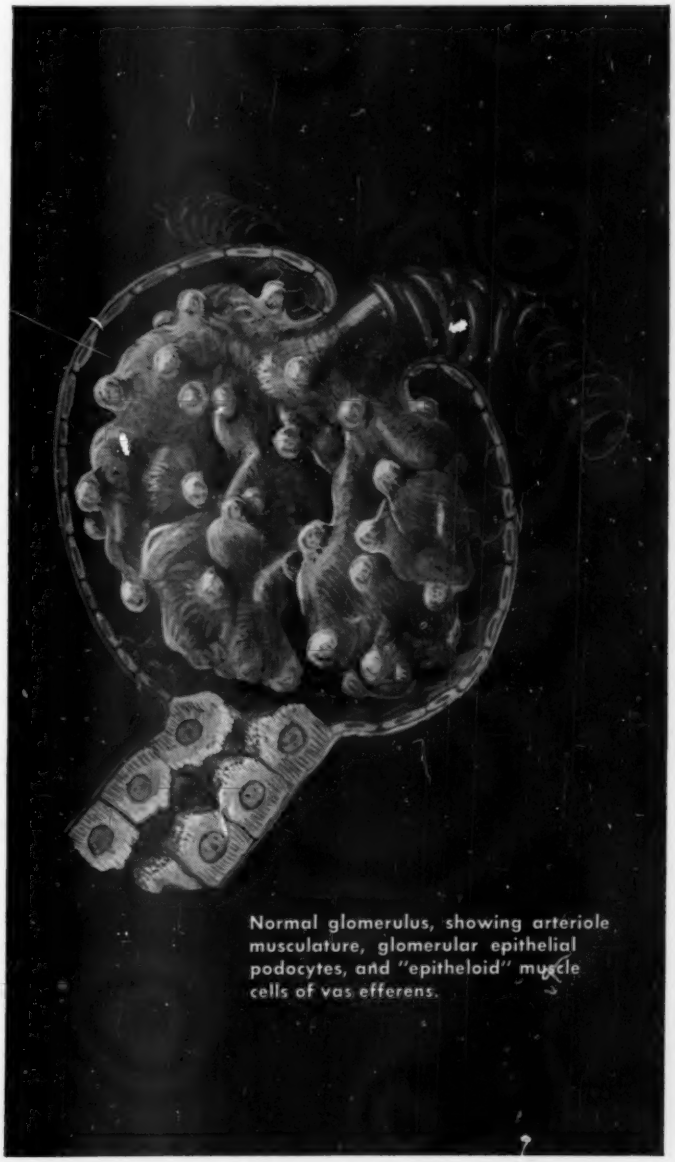

Normal glomerulus, showing arteriole musculature, glomerular epithelial podocytes, and "epitheloid" muscle cells of vas efferens.

1. Settel, E.: Rolicton® (Aminoisometradine), a New, Nonmercurial Diuretic, Postgrad. Med. *21*:186 (Feb.) 1957.
2. Assali, N. S.: Personal communication, May 28, 1956.

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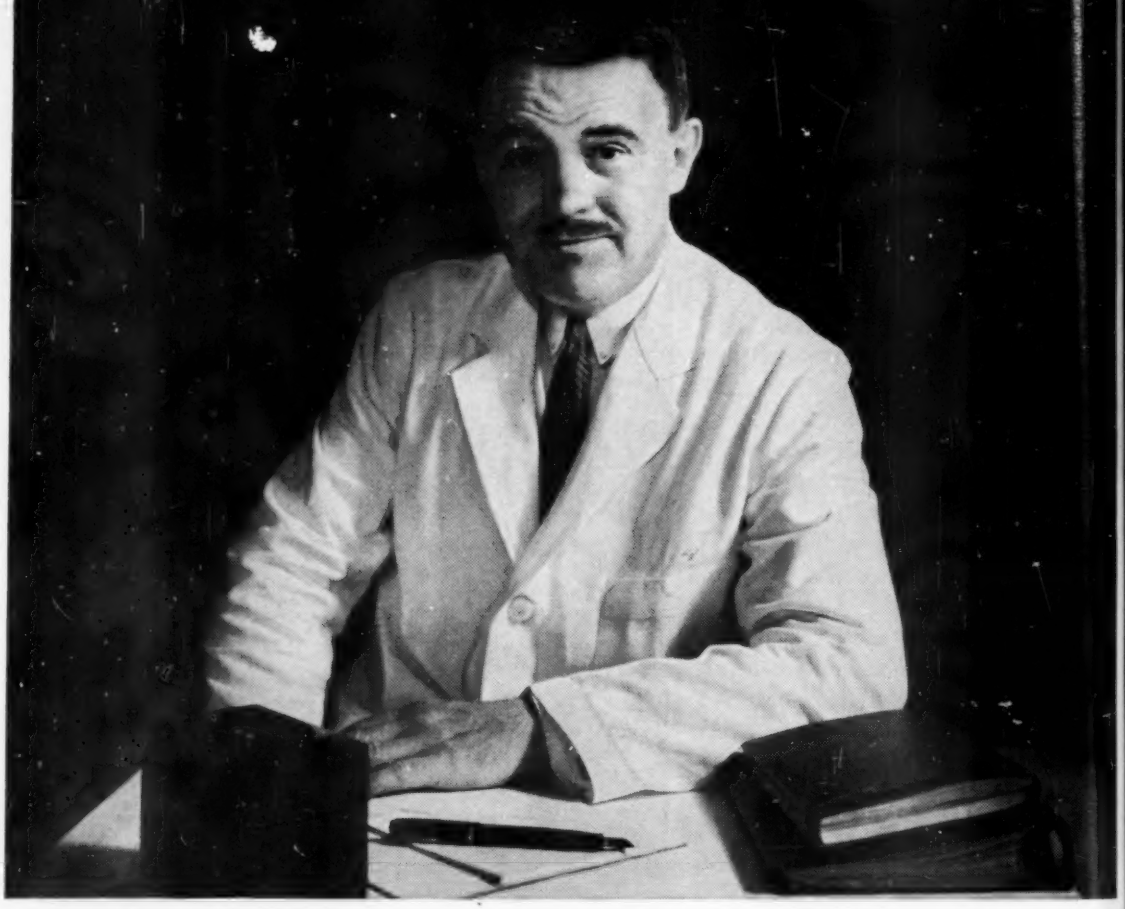

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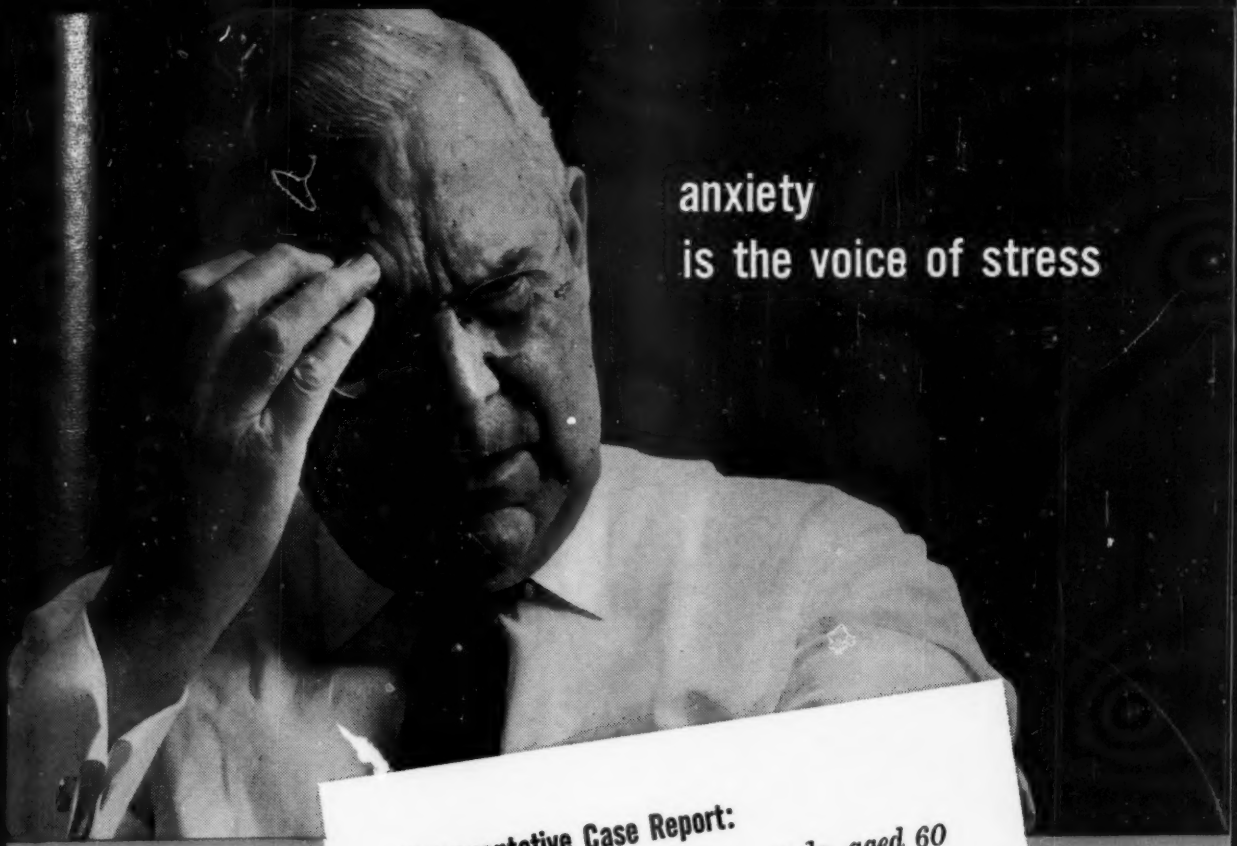

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1 Braveman, W. S.; Dexter, R. S., and Rubin, A. L.: Diamox (Acetazolamide) as an Oral Diuretic in Ambulatory Cardiac Patients. Am. Heart J. 54:284-290, 1957.

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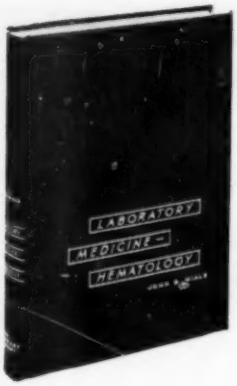

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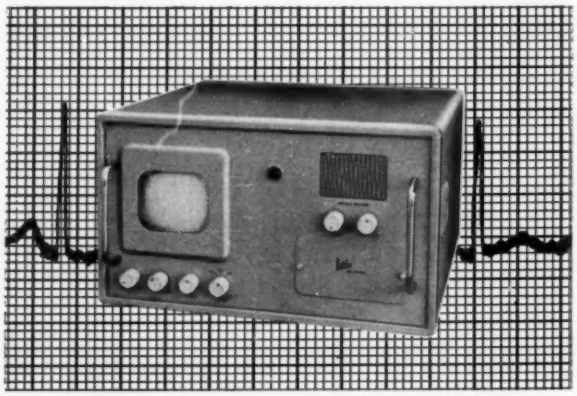

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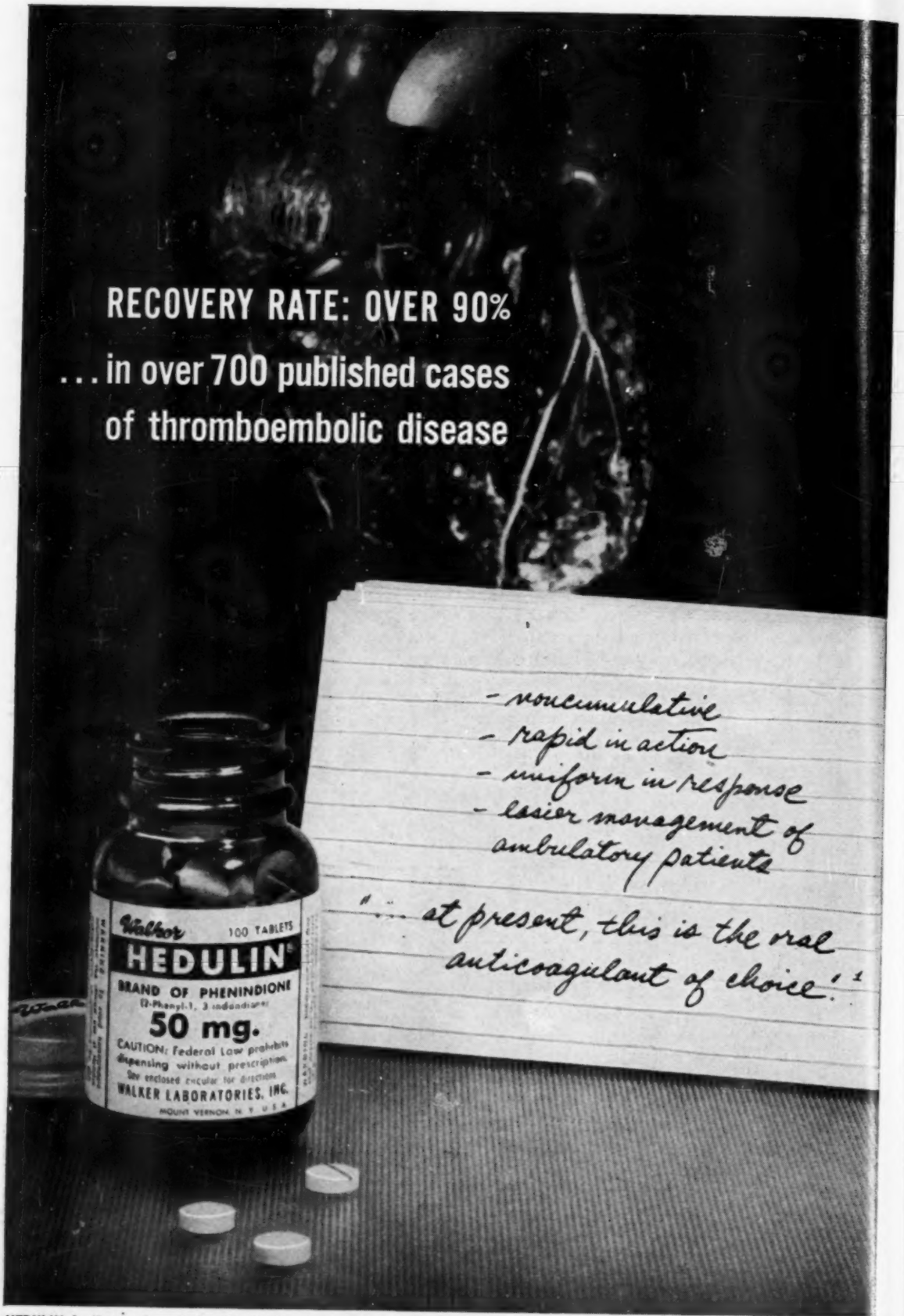

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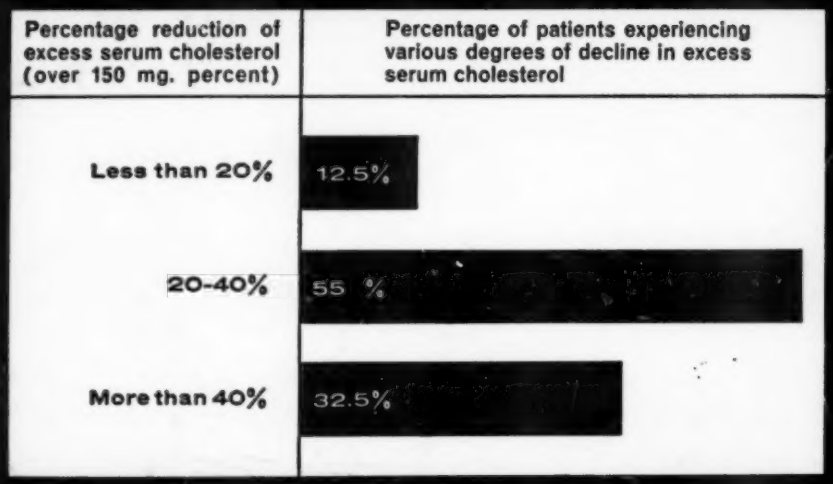
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